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Foreword

A major part of this book is the result of the work of a group of people from different disciplines who agreed to work together in better understanding the pathophysiology of tinnitus and in searching a cure for it.

Often - not only in science – progress and discovery have initiated from the efforts of a small group of people with little means but with creativity and enthusiasm.

In the 50's small “Cinecittà” in Rome surprised the Moguls of Hollywood and produced artists like Rossellini, De Sica and Fellini. A small movie studio but a big school nearby, where students could interact with artists and writers and directors with just one aim: do nice movies.

In other words a group of people working with the right model, the right dynamics and for the right reasons.

As giant pharmaceutical companies take less risks and focus more and more on manufacturing and marketing, small but efficient groups continue to have an important role in the structuring and creation of new solutions for old pathologies.

As founder and sponsor of the Tinnitus Research Initiative (TRI), as well as other organisations, I have come to realize that if one succeeds in gathering a group of motivated people who think and act correctly in a collaborative way and for the right reasons, you get back much more than you have given, whether it is in time, experience or money.

I believe that the organizers of TRI have gathered such a group.

The practical result of their work will not be visible for a few more years, but I think and wish they will succeed.

As a tinnitus sufferer, thank you!

Principality of Monaco, July 2007
Matteo de Nora

Preface

Tinnitus: Pathophysiology and Treatment

There are two main types of tinnitus, objective and subjective tinnitus. Objective tinnitus is caused by sounds generated in the body and transmitted to the ear. Subjective tinnitus is caused by abnormal neural activity. Objective tinnitus is rare but subjective tinnitus is a frequent disorder that occurs with different severity. There are many forms of subjective tinnitus; it can be just noticeable, an annoyance or it can reduce the quality of life by impairing the ability of intellectual work, making it difficult to sleep, and tinnitus can lead to suicide. There are no objective tests that can measure subjective tinnitus, and the only person who can assess the tinnitus is the person who has the tinnitus. This is one of the aspects of subjective tinnitus that is similar to central neuropathic pain.

In general, studies show that the incidence of subjective tinnitus increases with age from approximately 5% at young age (20–30 years) to approximately 12% for individuals above the age of 50 years but available data regarding the prevalence of tinnitus varies between studies. Bothersome tinnitus is infrequent at young age becoming increasingly frequent with age, reaching 12–14% for people at age 65 and older. There are many risk factors for tinnitus such as hearing loss, including age-related hearing loss (presbycusis) and tinnitus may follow after exposure to noise, administration of ototoxic antibiotics and cytostatics, infectious diseases and trauma to the auditory nerve are also risk factors.

It is generally agreed that subjective tinnitus is not a disease but a symptom and the many forms of tinnitus probably have different pathophysiology. For a long time it was believed that tinnitus arose from the ear and that the anatomical location of the physiological abnormalities that caused the tinnitus was the ear. However it was later understood that most forms of tinnitus was caused by abnormalities in the central nervous system and these abnormalities were often caused by expression of neural plasticity. Realizing the complexity of tinnitus has highlighted the importance of interdisciplinary research. The fact that most forms of tinnitus are disorders of the nervous system put emphasis on neuroscience in studies of tinnitus.

The first chapters in this book discuss the pathophysiology of subjective tinnitus. The anatomical locations of the physiological abnormality that cause the abnormal neural activity that give the sensation of sounds when no sound reaches the ear are discussed. The similarity between tinnitus and pain and various hypotheses for tinnitus are the subjects of other chapters. Evaluation of the results of animal studies is the topic of other chapters. Subjective tinnitus is often accompanied by abnormal perception of sounds and many have a lowered tolerance to sounds (hyperacusis). People who have tinnitus may experience an interaction with other sensory modalities (cross-modal interaction), such as with the somatosensory system. These matters are discussed in detail in the book.

Treatments that are available are medical and behavioral, and some use electrical stimulation of the skin, the ear or structures of the central nervous system. However, presently used treatments are often unable to relieve the tinnitus in a satisfactory way. This book discusses many different kinds of treatment and their efficacy and the different chapters describe new means and approaches to treatment of subjective tinnitus.

Most of the contributors to this volume participated in a conference held in Regensburg, Germany, 2006 that was sponsored by a newly formed private organization “The Tinnitus Research Initiative” the goal of which is to improve treatments for tinnitus through advances in the understanding of the pathophysiology of tinnitus. The organization promotes a collaborative interdisciplinary approach to research on tinnitus.

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CHAPTER 1

Tinnitus: presence and future

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Abstract: Tinnitus has many forms; it can be caused by sounds generated in the body (objective tinnitus) that reaches the ear through conduction in body tissue, but much more common is the tinnitus that occurs without any physical sound reaching the ear. Such tinnitus (subjective tinnitus) is a phantom sensation, where abnormal neural activity is generated in the ear, the auditory nerve, or the central nervous system. There are many forms of subjective tinnitus and it can occur with different severity. Subjective tinnitus often occurs in connection with hearing loss such as may occur after exposure to loud sounds (noise), or after administration of drugs such as certain antibiotics, but often no cause can be found. Tinnitus often occurs together with presbycusis and it can occur in deafness. Tinnitus is a part of the symptoms of Ménière's disease and individuals with vestibular Schwannoma almost always have tinnitus. Some individuals who have severe tinnitus hear sounds as distorted and some have hyperacusis (reduced tolerance to sounds) or phonophobia (fear of sounds). Tinnitus can be referred to one ear, or both ears, or to a location inside the head. The anatomical location of the physiological abnormality of chronic subjective tinnitus, however, is rarely in the ear but more often in the auditory nervous system. There are indications that the pathophysiology of unilateral and bilateral tinnitus is different. There is considerable evidence that expression of neural plasticity plays a central role in the development of the abnormalities that cause many forms of chronic subjective tinnitus. Expression of neural plasticity can change the balance between excitation and inhibition in the nervous system, promote hyperactivity, and it can cause reorganization of specific parts of the nervous system or redirection of information to parts of the nervous system not normally involved in processing of sounds (non-classical or extralemniscal pathways). Since there are many kinds of subjective tinnitus, search for a (single) cure for tinnitus is futile. Testing of new treatments is hampered by the fact that it is not possible to distinguish between different forms of tinnitus for which different treatments may be effective.

Keywords: tinnitus; neural plasticity; phantom sounds; hyperacusis; tinnitus treatment

Introduction

Tinnitus and auditory hallucinations are perception of sounds that occur in the absence of external sounds. Tinnitus can be divided into two broad

groups, objective and subjective tinnitus. Objective tinnitus is caused by sound generated in the body reaching the ear through conduction in body tissues (Møller, 2003a) (Chapter 22). The source can be turbulent flow of blood in an artery where there is a constriction, or it can be caused by muscle contractions. Unlike subjective tinnitus, an observer, using a stethoscope, can often hear

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objective tinnitus. Subjective tinnitus is meaningless sounds that are not associated with a physical sound and only the person who has the tinnitus can hear it. Subjective tinnitus is far more prevalent than objective tinnitus; this chapter will concern subjective tinnitus. Auditory hallucinations are meaningful sounds such as music and voices. Hallucinations are rare but occur in various forms of psychiatric disorders such as schizophrenia. This chapter will not discuss hallucinations.

Tinnitus can have different effects on an individual. It can be just minor nuisance or it can cause suffering by disturbing sleep, causing anxiety, and affective symptoms such as depression or phonophobia.

Subjective chronic tinnitus belongs to a group of phantom sensations (Jastreboff, 1990) similar to central neuropathic pain (see Chapter 4). Phantom sensations are not disorders but symptoms of various kinds of abnormalities in which expression of neural plasticity is involved. Paresthesia of the somatosensory system are similar “phantom sensations” as tinnitus. Phantom sensations rarely occur in other sensory systems but have been reported in vision (phosphene) and olfaction (phantosmia, or olfactory hallucinations) (Møller, 2003b). Little is known about phantom taste sensations except from certain medications that can cause odd sensations such as a metallic taste.

Severe tinnitus are often accompanied by abnormal perception of sound including an abnormal low tolerance for sounds (hyperacusis)¹ (Baguley, 2003) or distortion of sounds. Hyperacusis is common in traumatic head injuries, where it often occurs together with tinnitus and hypersensitivity to light. Sequella of meningitis, especially where appropriate treatment was delayed, may include similar symptoms of severe tinnitus and hyperacusis, often accompanied by severe hearing loss or deafness.

¹Different definitions of hyperacusis are in use and the term is sometimes used to describe abnormal perception of loudness. However, abnormal perception of loudness is a different anomaly known as “recruitment of loudness”, an audiologic term that is used to describe a condition that is common in people with cochlear hearing loss and which means that the loudness of a sound increases more rapidly than normal (Møller, 2006a).

Recently the term *misophonia* (Jastreboff and Jastreboff, 2006) has been suggested to describe dislike of sound. Phonophobia and misophonia are forms of intolerance that may regard specific sounds with emotional associations whereas hyperacusis is normally unrelated to the type of sound. Affective disorders such as depression and phonophobia may also accompany severe tinnitus and thereby tinnitus can result in suicide.

Several animal models of tinnitus have been created either by noise exposure or by administration of salicylate (aspirin). The use of animal models depends on the ability to detect when the animals perceive tinnitus and several different methods for that have been described (Jastreboff et al., 1988; Jastreboff, 1989; Bauer et al., 1999) (see Chapter 13).

It is unfortunate that the same name, tinnitus, is used for so many different disorders. This hampers both understanding of the pathophysiology of tinnitus and the treatment because it implies that it is possible to find *the* cause of tinnitus and *the* treatment for tinnitus. Central neuropathic pain is similar (see Chapter 4). Disorders of the vestibular system was earlier in the same category, but the introduction of specific names such as, for example, benign positional paroxysmal nystagmus (BPPN) and disabling positional vertigo (DPV) has greatly improved treatment and understanding of the causes of various symptoms from the vestibular system.

Characteristics of subjective tinnitus

Subjective tinnitus has many different forms and its severity and character varies widely. It can be localized (referred) to one side or both sides and it can be felt as coming from the center of the head. Some investigators divide tinnitus in three groups according to the way it is perceived: mild tinnitus, moderate tinnitus, and severe (disabling) tinnitus (Reed, 1960).

Mild forms of tinnitus rarely cause any problems; moderate tinnitus can interfere with intellectual work and sleep and often cause suffering. Severe tinnitus can have major effect on a person's entire life, making sleep difficult and intellectual work impossible.

Quantitative assessment of the intensity of tinnitus is hampered by the fact that tinnitus when matched to real sounds appear to have very low intensity even in individuals who report that their tinnitus is very loud. Fowler in 1943 reported that though patients described their tinnitus as very loud, yet the tinnitus could usually be matched at only 5–10 dB sensation level (SL) (Vernon, 1976) and that tinnitus is difficult to mask (Fowler, 1942; Reed, 1960; Vernon, 1976). This is an obstacle in an attempt to quantitatively evaluate tinnitus and in monitoring the results of treatment. Some investigators use a visual analog scale (VAS) to estimate the intensity of tinnitus. VAS is in extensive use in pain research and now often used for comparing tinnitus before and after treatment. The use of a VAS seems to produce results that agree better with tinnitus patients' own evaluation similar to what is experienced with attempts to quantify pain (Chapter 4). Some forms of tinnitus cause suffering while other forms do not. Tinnitus that involves suffering has also been called “bothersome tinnitus” (Chapter 44) or “problem tinnitus” by some investigators (Gerken et al., 2001). There are indications that suffering from tinnitus involves parts of the central nervous system (CNS) that are outside the auditory nervous system (Chapters 3 and 40).

Prevalence of subjective tinnitus

It is difficult to get a clear picture of the prevalence of tinnitus. The fact that tinnitus has many forms and that it has widely different severity has caused different studies of the prevalence of tinnitus to yield widely different results (Ahmad and Seidman, 2004; Hoffmann and Reed, 2004; Henry et al., 2005). Different studies have arrived at different values of prevalence (Hoffmann and Reed, 2004). For people of all ages the prevalence of tinnitus varied from 4.4% to 15.1%. All studies reviewed agreed that the prevalence is higher above the age of 50. In this age group the different studies reported prevalence between 7.6% and 20.1%. Most elderly people have some forms of tinnitus particularly when visiting in a quiet environment but it is disturbing for only some

individuals and only a few individuals suffer from the tinnitus.

The fact that the severity of tinnitus and pain can only be assessed by the patient and cannot be measured objectively is a source of uncertainty in epidemiologic studies. Most of the variations in the reported prevalence of tinnitus between different investigators are likely caused because investigators had different criteria for what they regarded as tinnitus, and also the inclusion criteria in some studies may have been biased. Individuals who have tinnitus but no noticeable problems do not seek medical assistance except for those individuals who are concerned that their tinnitus may be a sign of a severe disease such as a brain tumor. Most people over the age of 50 occasionally experience tinnitus but many do not find their tinnitus to be a significant problem. Some people who do find their tinnitus debilitating may have given up their attempts to find help from the medical profession.

Hyperacusis

Hyperacusis often is present together with tinnitus. Different definitions of the term hyperacusis are in general use (Jastreboff and Jastreboff, 2004). Some investigators have used the term hyperacusis synonymously to the term hyperesthesia, which for the somatosensory system is defined as “abnormal acuteness of sensitivity to touch, pain, and other sensory stimuli” (Stedman's Concise Medical Dictionary, 26th ed., Baltimore: Williams and Wilkins, 1997). Others have described hyperacusis as an abnormal, lowered tolerance to (any) sound (Baguley, 2003). We will use the definition proposed by Baguley in this chapter.

Hyperacusis often occurs together with tinnitus but may also occur alone. Hyperacusis occurs in most individuals with Williams-Beuren's syndrome (WBS) (Gothelf et al., 2006) (infantile hypercalcaemia), a genetic disorder that is characterized by multiple congenital anomalies including cardiovascular disorders, mental retardation, post-natal growth retardation, and facial anomalies. Hyperacusis also often occurs as a sequel to meningitis and traumatic head injuries and together

with Ramsay-Hunt syndrome and Lyme disease. Discomfort from loud sounds and even fear of sounds (phonophobia) occurs in autism.

Cause of tinnitus

Several layers of complexity are involved in the pathophysiology and the cause of tinnitus and it is rarely known what causes an individual's tinnitus (idiopathic tinnitus). Hearing loss such as from noise exposure or from presbycusis is often followed by tinnitus but not always. Administration of ototoxic substances such as certain antibiotics, diuretics (furosemide), salicylate, and quinine can result in tinnitus. Disorders that affect the CNS such as meningitis, encephalitis, and strokes are often accompanied by tinnitus (and hyperacusis). Traumatic brain injury of various kinds is often accompanied by tinnitus and abnormal perception of sounds and visual stimuli. Herpes infections such as the Ramsey-Hunt syndrome and different forms of injury to the auditory nerve such as surgically induced injuries are often followed by tinnitus.

Other forms of injury to the auditory nerve are often accompanied by tinnitus (Møller, 2006a) and close contact between the auditory nerve and a blood vessel may also cause tinnitus (Chapters 38 and 39).

Tinnitus often begins without any external or internal events can be identified. One possible reason may be the gradual deterioration of neural function that occur with age, characterized by decrease in number of functioning nerve fibers, which is a part of the age-related (normal) decrease in the reserves of the nervous system. Another age-related change includes increase in the variation in conduction velocity as has been shown to occur in the auditory nerve (Spoendlin and Schrott, 1989). Tinnitus may begin when these gradual changes have reached a certain critical level and this form of tinnitus is thus related to the occurrence of a specific event. This makes it difficult to identify the source of many forms of tinnitus.

Tinnitus is one of the three symptoms that characterize Ménière's disease. Individuals who have a vestibular Schwannoma almost always have

tinnitus. Tinnitus may accompany bodily disorders that affect the head such as temporomandibular joint (TMJ) disorders (Morgan, 1992) and certain forms of head and neck muscle spasm (Bjorne, 1993; Levine et al., 2003) (see Chapters 17 and 19). Such forms of tinnitus are known as somatic tinnitus (Chapter 10), and when the muscle disorders are resolved, the tinnitus usually also decreases or disappear.

Change in the function of the central nervous system

The changes in the function of the auditory nervous system that can cause tinnitus include altered balance between inhibition and excitation, reorganization of neuronal networks, changes in tonotopic maps, and rerouting of information. Altered balance between inhibition and excitation may cause hyperactivity.

The cochlea normally provides not only excitatory input to the cochlear nuclei but also inhibitory input is abundant. When the cochlea is impaired both excitatory and inhibitory input to the cochlear nucleus is reduced (Casparly et al., 2005), but often inhibitory input is reduced more than excitatory input resulting in a shift in the balance between inhibition and excitation.

Tinnitus is often associated with injuries to the cochlear sensory cells or to auditory nerve fibers. Such injuries cause reduced input to central auditory structures, and in general, inhibitory synapses are affected more than excitatory synapses (Kim et al., 2004) thus creating the basis for hypersensitivity (Gerken et al., 1984) and hyperactivity (Chapter 2).

Deprivation of input to the cochlear nuclei such as has been studied in experimental animals by unilateral removal of one cochlea has been shown to cause a down-regulation of bilateral glycine receptors in the dorsal cochlear nucleus (DCN), the ventral cochlear nucleus (VCN), and the lateral superior olive, and glycinergic activity in the medial superior olive nucleus was strengthened (Suneja et al., 1998; Eggermont, 2005) (Chapter 2). Inhibition is strong in the DCN where fusiform cells receive focused glycinergic inhibiting inputs. Age-related loss of markers for glycinergic

neurotransmission in the DCN occur (Casparly et al., 2005). Loss or reduction of inhibition from the cochlea can also cause increased excitability in other nuclei of the ascending auditory pathways.

The abnormalities in the function of the nervous system that cause many forms of tinnitus are most often a result of expression of neural plasticity that may be brought about by abnormal input from the ear or through abnormal function of the auditory nerve, or by unknown causes (Møller, 2006b) (Chapter 3).

Deprivation of input may cause expression of neural plasticity that can change the relation between inhibition and excitation and protein synthesis (Sie and Rubel, 1992) and cause reorganization of the nervous system (Møller, 2006b), which may cause tinnitus (see Chapter 3). Deprivation of input may also alter temporal integration as shown in animals after deprivation of input (Gerken et al., 1991) and after exposure to loud noise (Szczepaniak and Møller, 1996b). In a similar way, temporal integration of somatosensory stimuli may be altered in individuals with signs of chronic central neuropathic pain (Møller and Pinkerton, 1997) (Chapter 4) (Møller, 2006b).

Anatomical location of the abnormality that cause the sensation of tinnitus

It is of fundamental importance to identify the anatomical location of the physiological abnormality that generates the neural activity that is perceived as tinnitus. Tinnitus is often referred to one ear or both or as coming from the inside of the head. This has resulted in focus on the ear as the location of the physiological abnormality that causes the tinnitus. There is evidence that injuries of cochlear hair cells can be involved in causing tinnitus, at least as a first stage of the development of chronic tinnitus, and there are indications that the auditory nerve may be the primary or secondary cause of some forms of tinnitus (Møller, 1984). However, it has become evident that most forms of severe tinnitus is generated in the CNS and many studies have found evidence that the abnormalities are caused by expression of neural plasticity. This means that the anatomical location of the

physiologic abnormalities have incorrectly been assumed to be the ear.

Some studies have involved the possible role of the olivocochlear bundle. The fact that tinnitus can occur after the auditory nerve has been severed is strong evidence that tinnitus can occur without involvement of the ear and that the anatomical site of the physiological abnormalities that causes the sensation of tinnitus is the CNS. It also means that most forms of tinnitus are not generated at the location where the symptoms are felt (the ear) thus similar to, for example, phantom pain. It was therefore a major step forward when it became understood that the neural activity that caused most forms of tinnitus was generated in the nervous system with or without the involvement of the ear. In studies of the role of the CNS in tinnitus the focus has mainly been on three different structures: the DCN, the inferior colliculus, (IC), and the primary and secondary auditory cortices. Indications that the DCN (Chapter 9), IC (Chapter 2), and the cerebral cortex (Chapters 8, 11, and 36) are involved in tinnitus have been presented by many investigators. Little attention has been given to the thalamus.

The neural activity that produces the sensation of tinnitus (see Chapter 3) differs between the different forms of tinnitus and it may be generated in neural structures that are not normally activated by sounds that reach the ear, which can occur because of rerouting of information (see Chapter 3).

Several studies in humans (Ma et al., 2006; Melcher et al., 2000) and in studies in animals (Szczepaniak and Møller, 1996b) indicate that the IC may be implicated in tinnitus in several ways (Chapters 2 and 3). Hyperactivity in the central nucleus of the IC (ICC) is a possible cause of tinnitus. Activation of the external nucleus of the IC (ICX) and the dorsal cortex (DC) of the IC that are parts of the non-classical pathways (earlier known as the non-specific or the extralemniscal pathways (Aitkin, 1986)) may be involved in tinnitus and cause rerouting of information to the non-classical pathways (Chapter 3).

Studies have indicated that the cerebral cortex in humans is implicated in some forms of tinnitus (Mühlnickel et al., 1998). The involvement of the auditory cortex has also been supported by studies

in which electrical or magnetic stimulation of the cerebral cortex have been able to affect tinnitus (Chapters 34, 35, and 36). Some studies using imaging techniques have found evidence of an abnormal activation of the auditory cortices and of the amygdala (Lockwood et al., 1998).

Little attention has been devoted to the thalamic auditory nucleus, the medial geniculate body (MGB), although inference from studies of pain indicates that the MGB may play an important role in some forms of tinnitus. Some of the results of stimulation of the auditory cerebral cortex may in fact have been caused by an effect on the MGB through the descending cortico-thalamic pathways.

The neurons in the DCN receive similar input from the auditory nerve as neurons in the two other parts of the cochlear nucleus, and the DCN has been extensively studied for its role in tinnitus (Chapter 9) (Kaltenbach, 2000; Kaltenbach and Afman, 2000; Kaltenbach et al., 2004) (see Chapter 9) (Levine, 1999). Many features of DCN hyperactivity that may be caused by lack of input are similar to those of tinnitus. Modulation of tinnitus by change of gaze (Cacace et al., 1994; Coad et al., 2001) and jaw movements (Pinchoff et al., 1998) may also be mediated by the DCN. The fact that the DCN receives input from the upper spinal cord (C₂) (Young et al., 1995; Kanold and Young, 2001), which normally has to do with movement of the pinna, may be important for its role in tinnitus. These connections may explain why electrical stimulation of the skin around the outer ear can modulate tinnitus in some individuals (Schulman et al., 1985) and why manipulations of muscles in the mouth (Bjorne, 1993) (Chapter 19) or the neck (Levine, 1999) (Chapter 17) can affect tinnitus. TMJ disorders are often accompanied by tinnitus (Morgan, 1992). Stimulation of C₂ affects neurons in the DCN, and muscle stretch was more effective than skin stimulation indicating that proprioception is important. That explains why stretching of muscles is more efficient in modulating tinnitus than brushing the skin, which means that proprioceptors have a larger influence on the DCN than skin receptors. Proprioceptive input to the DCN from neck muscles would mean that head position has

influence on DCN neurons (Kanold and Young, 2001).

Severing the fiber tract that constitutes the output of the DCN, the dorsal stria (stria of Monaco) in animal experiments had little effect on hearing indicating that the DCN normally does not seem to play an important role in hearing (Masterton et al., 1994). This does not mean, however, that the DCN is not involved in generating tinnitus. Normally the DCN seems to be involved in localization behavior rather than processing of sound stimuli (May, 2000). It is generally assumed that the DCN integrate sound localization information with head position.

It has been shown that there are connections between the trigeminal ganglion and the VCN (Shore et al., 2000) and stimulation of the trigeminal ganglion affect responses from single cells in the VCN (Shore et al., 2003) as well as in the DCN (Shore, 2005) (Chapter 10).

The pathophysiology of disorders that have bilateral symptoms are often different from those that have unilateral symptoms and there are many signs that the pathophysiology of unilateral tinnitus is distinctly different from that of bilateral tinnitus. The difference in the pathophysiology of unilateral and bilateral tinnitus can explain why microvascular decompression (MVD) is less efficient in treatment of bilateral tinnitus compared with unilateral tinnitus (Vasama et al., 1998) (Chapters 38 and 39).

Rerouting of information

Rerouting of information may cause structures of the CNS that are normally not involved in processing auditory information to become activated by sound stimulation. An example of such rerouting is an abnormal involvement of the non-classical (non-specific or extralemniscal) pathways. The fact that the perception of tinnitus by some individuals with severe tinnitus is affected by stimulation of the somatosensory system (Møller et al., 1992; Cacace et al., 1994) is a sign of involvement of the nonclassical auditory pathways. Neurons in the nonclassical auditory pathways respond to more than one sensory modality while neurons in the

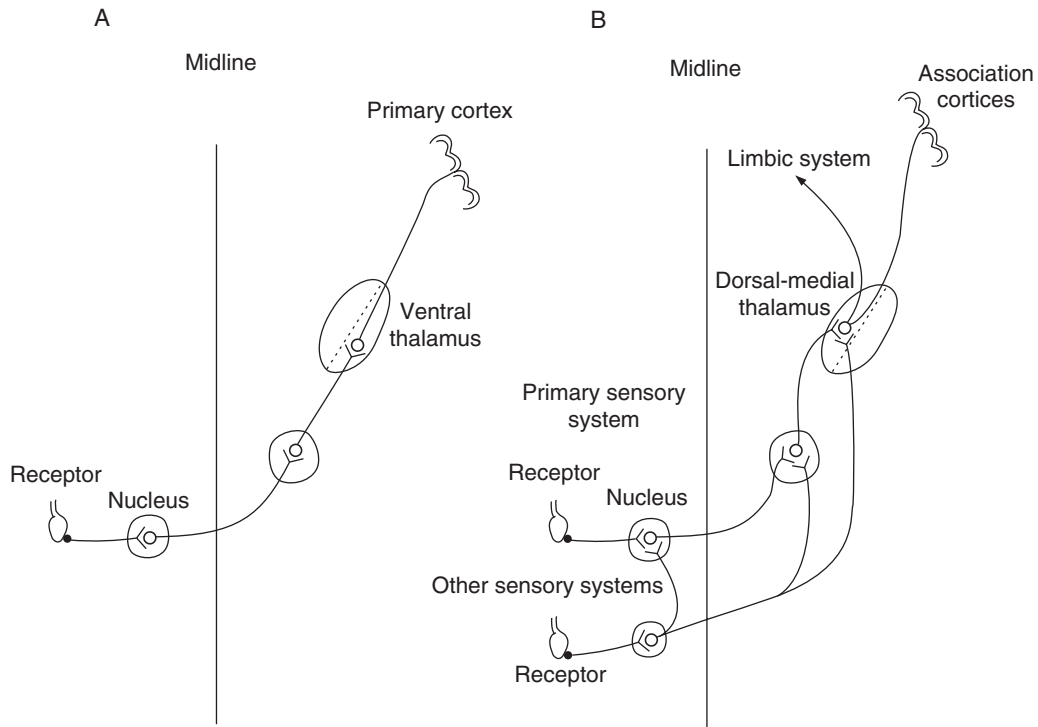


Fig. 1. Schematic drawing of the general outline of the ascending pathways of a sensory system emphasizing the difference and the similarities between the classical (A) and the non-classical pathways (B). (Note that the two receptors in B are from two different sensory systems, for instance auditory and somatosensory.) (Adapted with permission by Elsevier, from Møller, 2003b.)

classical pathways up to and including the primary auditory cortex only respond to auditory stimuli. This means that if only the classical pathways are activated, perception of auditory stimuli cannot be modulated by stimulation of other sensory system. If input from other senses can modulate perception of sound, it is taken as an indication of involvement of the nonclassical auditory system. This fact has been used as a test of the involvement of the nonclassical auditory pathways (Møller et al., 1992; Møller and Rollins, 2002) (Fig. 1).

The anatomical location where the results of somatic stimulation interact with auditory information is the ICX and DC of the IC (Aitkin et al., 1978). These nuclei are parts of the nonclassical auditory pathways, whereas the ICC is part of the classical ascending auditory pathways (Aitkin, 1986; Møller, 2003b). Animal experiments have shown that electrical somatosensory stimulation of the upper body is more efficient than stimulation of the lower body (Aitkin, 1986).

Risk factors for tinnitus

Known risk factors for tinnitus are age, exposure to noise, administration of certain drugs, Ménière's disease, vestibular schwannoma, head trauma, injuries to the auditory nerve, and cardiovascular disorders.

It is well known that tinnitus becomes more prevalent with age. While tinnitus is often associated with noise exposure, administration of ototoxic antibiotics, or hearing loss due to various causes such as age (presbycusis), these same conditions also often occur without tinnitus and tinnitus occurs in individuals who have none of these conditions. Although individuals with tinnitus often have hearing loss, some individuals with normal hearing have tinnitus. Silence can often cause tinnitus in individuals who do not experience tinnitus in a normal environment (Chapter 42). In fact many people, especially elderly, will experience tinnitus in silence such as in a sound insulated

audiologic test room with low ambient noise level and most people will experience tinnitus when in a silent room (anechoic chamber) (Tucker et al., 2005). This means that deprivation of input can cause acute tinnitus. Reduced inhibitory influence from the ear is assumed to cause this kind of tinnitus. Individuals with TMJ disorders often have tinnitus (Morgan, 1992), and TMJ is thus another risk factor for tinnitus. Tinnitus in connection with TMJ problems disappears when the TMJ disorder has been treated successfully (Morgan, 1992). This kind of tinnitus is assumed to be caused by abnormal stimulation of the somatosensory systems (trigeminal system) and it may have to do with stimulation of nerve fibers of the C₂ root of the spinal cord, stimulation of which has been shown to influence cells in the DCN (Young et al., 1995, see p. 8). Problems with neck muscles (Levine, 1999) (Chapter 17) and muscles of the mouth (Chapter 19) are also often accompanied by tinnitus thus indicating that such problems are risk factors for tinnitus.

Treatment of tinnitus

Progress in so many areas of care of the sick has depended on studies of epidemiology, basic research (pathophysiology), clinical research, and experience of different kinds of treatment. Progress in treatment of tinnitus may come from basic science that provides increased knowledge about the changes in the ear and the nervous system that underlies tinnitus. Areas of basic science that may contribute to understanding of the pathophysiology of tinnitus include hearing science, neuroscience, biochemistry, molecular biology, epidemiology, and genetics. Exploring similarities between some forms of tinnitus and some forms of neuropathic (physiological) pain may provide suggestions about treatments of some forms of tinnitus. Inability to distinguish between different forms of tinnitus and lack of adequate objective diagnostic methods are obstacles in the management of the tinnitus patient (see Chapter 22). It is an obstacle in treatment of tinnitus that patients do not have a clear direction regarding which specialty of the medical profession to consult. At the present state of understanding of the pathology of tinnitus,

treatment of the various forms of tinnitus would benefit from involvement of several clinical specialties such as neurology, psychiatry, psychology, audiology, and otolaryngology.

Progress in treatment may also come from serendipitous observations, and from clinical experience of treatment of patients with other disorders when these patients also have tinnitus. Many effective treatments of a wide range of disorders have been discovered in that way. However, as Louis Pasteur said “Chance favors only the prepared mind.” Therefore only the prepared clinician can take advantage of such incidences. To facilitate serendipitous discoveries that can benefit treatment of tinnitus, physicians within all specialties of medicine should have basic knowledge about tinnitus and medical schools should be encouraged in teaching the basics about tinnitus. Even though there are many forms of pain, there are treatments (analgesics) that can reduce or eliminate most forms of pain. There is no known comparable medication that can benefit patients with different forms of tinnitus.

The fact that tinnitus has many forms and that there are no diagnostic methods that can separate individuals with different forms of tinnitus are major obstacles in testing possible treatments for tinnitus.

Now, different forms of treatment are in clinical use such as tinnitus retraining therapy (TRT) (Chapter 40) and other forms of therapies that use counseling together with sound stimulation (Chapters 41, 42, and 44). Use of surgical treatment such as MVD (Chapters 38 and 39), stimulation of the cochlea through cochlear implants (Chapter 33), and stimulation of the auditory cortex (Chapters 34, 35, and 36) are beginning to be used in some specialized clinics.

Many substances have been tried for treatment of tinnitus (Chapters 23, 24, 25, 27, and 30). Some are based on evidence that reduced inhibitory influence is involved in some forms of tinnitus and it is known that the number of gamma aminobutyric acid (GABA)-immunoreactive neurons in the auditory nuclei decreases with age (Casparly et al., 1990, 1999) (Chapter 2). Efforts to restore or enhance the function of these receptors have been made using administration of substances such as

benzodiazepines that interact with (enhance) GABA_A receptors. Substances that increase the level of GABA in the CNS (Vigabatrin, Brozoski et al., 2007; Gabapentin, Chapter 27) have been tried in humans and in animal experiments.

It has also been hypothesized that GABA_B receptors were involved in some forms of tinnitus and the GABA_B agonist, baclofen, has been tried in humans and in animal models of tinnitus. While animal studies have been encouraging (Szczepaniak and Möller, 1996a), attempts to use baclofen in treatment of tinnitus showed a non-significant difference from placebo (Westerberg et al., 1996). However, baclofen provided improvements in 9.7% after 3 weeks treatment compared with 3.4% for placebo. Again, 2.5 times as many had benefited from baclofen as placebo; while this difference was not significant, the results of the trial may indicate that the population that was studied might have had several different kinds of tinnitus (see p. 4). The beneficial effect on one of these kinds of tinnitus may have reached a level of significance if studied alone.

Serotonergic activity is affected by administration of salicylate that can cause tinnitus (Chapter 2), and that may explain why selective serotonin re-uptake inhibitors (SSRIs) that manipulate the serotonin can, however, also increase tinnitus (Chapter 24). The *N*-methyl-D-aspartic acid (NMDA) (glutamate) receptor is most likely also involved in tinnitus, as it is in many forms of central neuropathic pain. However, attempts to use NMDA receptor inhibitors (such as the MK801 experimental drug) in treatment of pain have not been successful (Møller, 2006b). While it has been shown that aspirin activate cochlear NMDA receptors and that application of an NMDA receptor antagonist at the round window abolishes tinnitus (Chapter 12), administration of an NMDA antagonist, flupirtine, a drug that is similar to Memantine, had little effect on tinnitus in animal experiments (Salembier et al., 2006). Memantine, used to treat neuropathic pain and Alzheimer's disease, acts both on the glutamate and the cholinergic systems. The drug suppresses glutamatergic transmission in hair cells and it is known from animal studies that salicylate acts on the glutamate system in hair cells (Lobarinas et al.,

2006). More exotic substances such as Acamprosat, a drug used for treatment of alcohol dependence and which is an antagonist to glutamate and an agonist to GABA receptors, have been tried in treatment of tinnitus with some success (Chapter 25). The fact that motor systems are involved in some forms of tinnitus has inspired the tests of substances that affect the motor systems, such as botulinum toxin (Chapter 31).

The effect of lidocaine on tinnitus has been studied by many investigators (Chapter 28) but the fact that it has to be administrated intravenously makes it unsuitable for general practical use in treatment of tinnitus. Lidocaine, a local anesthetic with complex action on the CNS, is primarily a sodium channel blocker (see Chapter 28). Attempts to find drugs with similar beneficial effect on tinnitus and which can be administrated orally have not been successful. Tocainide was developed with that in mind but its effect was questionable and it has severe side effects (Emmett and Shea, 1980; Lenarz, 1986). The benefit of using dietary supplements such as vitamins and minerals in treatment of tinnitus is controversial (see Chapters 26 and 29).

Electrical stimulation of the cochlea (Cazals et al., 1978; Rubinstein et al., 2003) is one such attempt that has been tried with some success. In people with hearing loss, electrical stimulation of the cochlea can suppress tinnitus (McKerrow et al., 1991; Miyamoto and Bichey, 2003; Rubinstein et al., 2003) (Chapter 33), and even in patients with near normal hearing and tinnitus (Sininger et al., 1987).

Sound stimulation and psychological treatment (counseling) such as the TRT (Jastreboff and Jastreboff, 2000) (Chapter 40), tinnitus habituation therapy (Hallam et al., 1984), tinnitus activities treatment (Chapter 41) (Tyler and Baker, 1983) have been shown to be beneficial to individuals with some forms of tinnitus.

More recently, electrical stimulation of the cerebral cortex (Plewnia et al., 2003, 2007; De Ridder et al., 2005; Kleinjung et al., 2005) (see Chapters 34, 35, and 36) has shown ability to alleviate some forms of tinnitus. These are thus similar treatments to what has been in use for treatment of central neuropathic pain such as transderm electric

nerve stimulation (TENS), dorsal column stimulation, thalamic stimulation, premotor cortex stimulation, etc. (Melzack and Wall, 1999). Thalamic stimulation has not been described for treatment of tinnitus but it is possible that electrical (and magnetic) stimulation of the cerebral auditory cortex acts on the thalamus through the cortico-thalamic tract.

Attempts to influence neurons in the DCN by electrical stimulation of the skin behind the ear has shown beneficial effect on tinnitus (Schulman et al., 1985). This implies activation of nerve fibers of the C₂ root, stimulation of which is known to affect the activity in the DCN (Young et al., 1995; Kanold and Young, 2001).

However, also electrical stimulation on other location on the body such as the median nerve (Møller et al., 1992) has been shown to modulate tinnitus in some individuals. This may be achieved through different mechanism. The ICX and DC of the IC receive input from the dorsal column nuclei (Aitkin, 1986), and there is evidence that the ICX and DC are involved in the nonclassical auditory pathways and thereby such stimulation may influence activity in the nonclassical auditory pathways (Møller et al., 1992).

The MVD operation on the auditory nerve intracranially is an effective treatment for some patients with tinnitus (Chapter 38) (Møller et al., 1993). MVD is also an effective treatment for some pain disorders of cranial nerves V and IX, and of nervous intermedius (Møller, 1998). The success rate of this form of treatment for tinnitus depends on the time the individual has had symptoms and the success has been shown to be much higher in women than in men (55 vs. 29%) (Møller et al., 1993).

Clinical trials for treatment of tinnitus

Rigorous studies of the efficacy of medications for tinnitus are few (Dobie, 1999) (Chapter 48), and many are case reports and anecdotes. Double blind tests for determining the efficacy often indicate that a drug has a low degree of efficacy over placebo (Robinson et al., 2005) (Chapter 24).

The heterogeneity of tinnitus complicates clinical trials of new treatments and it may make the

results to be misleading because the tinnitus of the different participants in such trials are likely to have different pathophysiology and therefore not amendable to the same treatment. Currently established test criteria (double blind) for new treatments are therefore not suitable for tinnitus because it is not possible to distinguish between tinnitus with different pathophysiology, and the participants in trials inevitably would have different forms of tinnitus. Treatments may have been discarded because of that, which is unfortunate if the treatment is beneficial to patients, which must be the goal of treatment, and not to satisfy some scientific criteria. If the treatment that is tested is 80% effective in one form of tinnitus that has a 20% representation in the study, the study will show an efficacy of 16%, which is not impressive and most likely will lead to discarding of the treatment as ineffective. That means that the samples of individuals who have a large likelihood of benefit have often been diluted by individuals with other forms of tinnitus (that produce similar symptoms) and thereby distort the results of trials of treatments.

Interpretations of trials of the efficacy of a drug in treatment of diseases that have one single cause, such as, for example, pneumonia caused by bacterial infections, are straightforward and the effect of treatment can be validated without being influenced by any noticeable placebo effect. Trials of the efficacy of treatment for complex and poorly defined disorders such as tinnitus and central neuropathic pain are difficult to design and the results of such trials are difficult to interpret and often such trials give controversial results when repeated by other investigators.

The considerable placebo effect of many of the treatments that have been tried for tinnitus may be regarded to be an obstacle in evaluating results of trials of efficacy of treatment but it supports the experience that counseling is an effective component of treatment of many forms of tinnitus (see Chapters 40 and 41).

If a patient with tinnitus feels benefit from a specific treatment despite the treatment has not received the scientific certificate of effectiveness or other patients with tinnitus do not experience the same benefit, should the treatment not be

continued on that patient? Whether the cause of the beneficial effect is called placebo effect or an unusual incidence is irrelevant to the patient, but an authoritative denial of the beneficial effect from the patient's physician can make the patient terminate the treatment.

Involvement of the sympathetic nervous system

Sympathetic nerve fibers may liberate noradrenaline that terminate near hair cells in the cochlea (Densert, 1974) and these may sensitize hair cells upon increased activity of the sympathetic nervous system (see Chapter 4). The sympathetic nervous system may also be involved in noise induced hearing loss (temporary threshold shift (Hildesheimer et al., 1991)) that often is associated with tinnitus. Tinnitus is related to stress as indicated by a study that found that cortisol reactivity to psychosocial stress is blunted in tinnitus sufferers (Hebert and Lupien, 2007). It was shown a long time ago that sympathectomy can relieve tinnitus in patients with Ménière's disease (Passe, 1951).

Future

For many years tinnitus was regarded as an auditory disorder and because it was often referred to the ear, the ear became the focus of studies of the pathophysiology of tinnitus and for the search of treatment. Recent studies and experience have shown that tinnitus is far more complex and that the anatomical location of the physiological abnormalities that cause the tinnitus is instead the CNS for most forms of subjective tinnitus. Implicating the CNS in the generation of the abnormal nervous activities that cause tinnitus was a major step forward and this progress was achieved by researchers who were "thinking outside the box." There is no doubt that more of that kind of thinking is what can bring important progress in the future regarding understanding of the pathophysiology of tinnitus and regarding development of effective treatments.

More efficient organization of research will facilitate research and search for better treatment.

Because of its complexity and diversity individual patients with tinnitus would benefit from a multidisciplinary approach regarding their treatment. Treatment and research on tinnitus therefore would benefit from a multidisciplinary approach involving neurologists, psychiatrists, and psychologists in addition to audiologists and otolaryngologists. The clinicians of these different disciplines should be educated about the neurophysiologic basis for tinnitus and the basic scientists should be educated about clinical aspects of tinnitus. It is also important that clinicians in other fields have an understanding of tinnitus so that they can be prepared for unforeseen events that may suggest useful treatment methods.

Researchers who work on tinnitus would benefit from being acquainted with progress in other fields of medicine. Many forms of tinnitus have similarities with different forms of neuropathic pain especially chronic central neuropathic pain (Chapter 4) (Møller, 2006b). Tinnitus is often associated with different forms of affective symptoms and it would be interesting to know if that is associated with activation of specific CNS structures. For example, it is known that inescapable and escapable pain use different parts of the periaqueductal gray (PAG) (Keay et al., 2001; Lumb, 2002). It would be interesting to know if there is a similar anatomical separation of different forms of affective disorders that occur together with tinnitus.

Conclusion

The pathophysiology of the different forms of tinnitus is far more complex than earlier assumed, and each one of the many different forms of tinnitus may have different pathophysiology and consequently requires different kinds of treatment to obtain the best benefits. The fact that tinnitus is not a single disease and that there are no methods available that can differentiate between tinnitus of different causes is an obstacle for diagnosing tinnitus and for treatment. It is also an obstacle in testing the efficacy of treatments because it is not possible to assemble a group of participants who have the same form of tinnitus for studies of the efficacy of treatments. It was an important step

forward when it became documented that the anatomical location of the physiological abnormality that cause the tinnitus was not always the ear but the CNS. Understanding that expression of neural plasticity is the cause of many forms of tinnitus or at least play an important role in creation of the neural activity that plays an important role in causing tinnitus was equally important.

Abbreviations

BPPN	benign positional paroxysmal nystagmus
CNS	central nervous system
DC	dorsal cortex (of the IC)
DCN	dorsal cochlear nucleus
DPV	disabling positional vertigo
GABA	gamma aminobutyric acid
HFS	hemifacial spasm
IC	inferior colliculus
ICC	central nucleus (of the IC)
ICX	external nucleus (of the IC)
MGB	medial geniculate body
NMDA	<i>N</i> -methyl-D-aspartic acid
MVD	microvascular decompression
SL	sensation level
TENS	transderm electric nerve stimulation
TMJ	temporomandibular joint (disorder)
TRT	tinnitus retraining therapy
VAS	visual analog scale
VCN	ventral cochlear nucleus
WBS	Williams-Beuren's syndrome

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CHAPTER 2

Pathophysiology of tinnitus

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Abstract: Guided by findings from neural imaging and population responses in humans, where tinnitus is well characterized, several morphological and physiological substrates of tinnitus in animal studies are reviewed. These include changes in ion channels, receptor systems, single unit firing rate, and population responses. Most findings in humans can be interpreted as resulting from increased neural synchrony.

Keywords: spontaneous firing; neural synchrony; neurotransmitters

Introduction

Tinnitus is a percept that is well characterized in humans and also in some animal models. Here the approach to the pathophysiology of tinnitus will be to start with human tinnitus sufferers and to find differences in cochlear and brain function with those that do not suffer tinnitus. The available methods range from otoacoustic emissions to probe the cochlea, evoked potentials or evoked magnetic fields to reflect synchronous brain activity, and forms of functional imaging such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) that are largely reflecting the number of active neurons and their firing rates (Mukamel et al., 2005). A caveat in all these investigations is that tinnitus is most frequent in individuals with hearing loss, and this in itself causes changes in the cochlea (by definition) and in the brain (Don et al., 1998; Oates et al., 2002). Age typically introduces additional changes in the central nervous system (Tremblay et al., 2003) as does gender (Don et al., 1993). Thus, the tinnitus and non-tinnitus groups should

preferably be matched for hearing loss, age and gender. Another caveat is that individual differences in evoked potential amplitude and functional images are often so profound that it is impossible to interpret the small changes observed. Therefore, studies where individuals serve as their own controls (unilateral tinnitus, gaze-induced tinnitus that can be controlled) are popular but the results may not be generalized easily. Furthermore, tinnitus as a percept is likely to depend on activity in the auditory cortices, even if the tinnitus generating structure is more peripheral. It is therefore useful to distinguish the tinnitus generation site from the site with the initial pathology, i.e., hair cell loss in the cochlea. We will call the tinnitus generation site, i.e., the site that is most peripheral in the auditory nervous system and that shows an accepted neural correlate of tinnitus, the ignition point (Eggermont, 2006). Here we have temporally neglected the important role of centrifugal cortical activity that, with some time delay, can cause changes in more peripheral structures. We will, as many others have done, equate the strength of the tinnitus sensation with the amount of deviance of the studied correlate from the norm. Correlates could for instance be the amplitude of evoked potentials, the size of the change in activated brain

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regions, or the incidence of spontaneous otoacoustic emissions.

Imaging studies in humans

PET studies in gaze-induced tinnitus suggest various correlates such as regional cerebral blood flow (rCBF) increase in the temporal-parietal auditory association areas (Brodmann area: BA 22, 40, 42) but not in primary auditory cortex (PAC) (Giraud et al., 1999) and in addition activation in the auditory lateral pontine tegmentum (Lockwood et al., 2001). Absence of activation in PAC rules out significantly increased spontaneous firing rate (SFR) but does not rule out increased neural synchrony as a correlate of tinnitus. In fMRI studies of gaze-induced tinnitus (Cacace et al., 1996) foci of activity in the tinnitus patient were localized in the superior colliculus and frontal eye fields in cortex. Presently it is not clear whether this reflects activity related to the motor act (gaze) that induces tinnitus or to the percept of tinnitus itself. In patients able to modulate the loudness of their tinnitus by oral facial movements the loci of activity were in the auditory cortex (AC) contralateral to the ear in which the tinnitus was perceived as well as in limbic structures (Lockwood et al., 2001).

Lidocaine infusion, which temporally suppresses tinnitus, produced equally likely increases or decreases in rCBF, but the changes were always larger for increases in the right temporal lobe of the auditory association cortex (Reyes et al., 2002), and this unilateral activation pattern suggests that the tinnitus originates centrally rather than peripherally. This is because for unilateral stimulation of a normal hearing subject there are always comparable changes in both hemispheres (Reyes et al., 2002). PET studies in groups of tinnitus patients with either Lidocaine or with suppression of tinnitus by masking suggest that the baseline cortical activity in the right hemisphere regardless the lateralization of the tinnitus can be abnormally high in individuals with tinnitus (Mirz et al., 1999).

Using fMRI to determine the effect of tinnitus on the activity in the inferior colliculus (IC), Melcher et al. (2000) found a specific effect of masking noise: in unilateral tinnitus binaural noise

produced an abnormally low further activation in the IC contralateral to the tinnitus ear. Since the amount of activation was calculated by comparing the brain oxygen level dependent (BOLD) response in the noise-masking condition to that without masking (but with tinnitus), one can interpret this by assuming that the tinnitus produces increased activation of the IC and that additional noise can only produce very little extra activation in the IC. Alternatives are that the noise masks the tinnitus and thus reduces its loudness and consequently its effect on IC activity. This finding suggests that neurons in the IC in individuals with tinnitus have a high-spontaneous activity. The authors noted that increased neural synchrony without increased SFR could not produce this effect.

Evidence for structural changes in individuals with tinnitus was found exclusively in the right posterior thalamus (including the medial geniculate body, MGB) where gray matter concentration was increased (Muhlau et al., 2006). This could point to increased dendritic arborization, potentially accompanied by increased synaptic density and the potential for increased spontaneous activity. It is interesting that the right auditory cortex, to which the right MGB projects, showed larger increases in activity compared to the left one.

Evoked potential or magnetic field recordings in humans

The generation of tinnitus in many individuals is associated with decreased input to the auditory system caused by hearing loss. Various sources of evidence indicate that deprivation of primary auditory input leads to a slow-wave mode functioning of the central nervous system, i.e., analysis of electroencephalogram (EEG) signals shows an enhanced power in the delta frequency range (<4 Hz). An example of such a condition is slow-wave sleep, during which thalamic (and thus also cortical) centers are partially *cut off* from input from prethalamic relays. This condition leads to a hyperpolarization of thalamocortical cells that activates sodium and potassium currents, gradually depolarizing the cell. The depolarization in turn triggers a calcium-mediated low-threshold

spike burst. The frequency of this hyperpolarization spike-burst cycle is approximately in the delta to theta frequency range. Because of the cortico-thalamic connections, coherent slow-wave oscillations are also seen on a cortical level. The spontaneous cortical neuronal activity recorded as the magneto-encephalogram (MEG) in a group of individuals with tinnitus is characterized by a marked reduction in alpha (8–12 Hz) power together with an enhancement in delta (1.5–4 Hz) as compared to a normal hearing control group. This pattern was especially pronounced for temporal regions. Moreover, correlations with tinnitus-related distress revealed strong associations with this abnormal spontaneous activity pattern, particularly in right temporal and left frontal areas (Weisz et al., 2005a).

Ever since it was suggested that phantom limb pain was associated with changes in the topographic map in sensorimotor cortex (Flor et al., 1995), and that similar map changes in AC could underlie tinnitus (Mühlnickel et al., 1998) the search has been on for an unambiguous demonstration of such map changes. Most of the techniques used are based on the MEG and the maps are constructed on basis of equivalent dipole source locations for a series of frequencies. Albeit that this technique is fraught with pitfalls for those based on the N_{100} component because of contributions from multiple areas with opposite tonotopic gradients (Lütkenhöner et al., 2003b), it nevertheless suggests that consistent changes do occur. It appears that mapping based on middle latency responses (MLRs) that originate in PAC is more reliable (Lütkenhöner et al., 2003a). Diesch et al. (2004) using the steady-state evoked magnetic field that originates exclusively in PAC found enhanced activity in individuals with tinnitus compared to normal hearing controls. The enhancement correlated with the perceived intensity and intrusiveness of tinnitus. Wienbruch et al. (2006) used the 40-Hz auditory steady-state response (SSR) that also originates in PAC to compare the tonotopic frequency representations between individuals with chronic tinnitus and hearing impairment and normal hearing controls. The SSR frequency gradients were attenuated in both hemispheres in individuals with tinnitus. Dipole power

was also elevated in tinnitus, suggesting that more neurons responded synchronously to the 40 Hz sound envelope. The altered frequency representations in tinnitus may reflect a loss of intracortical inhibition in partially deafferented frequency regions of the PAC after deprivation of input caused by cochlear injury. It is of course not clear if the map changes would have been different in a group of individuals with the same hearing loss but without tinnitus. The intricate interaction between hearing loss and tinnitus makes this difficult to study.

Attias et al. (1993) found that in individuals with tinnitus the event-related potentials (ERPs) (N_{100} , P_{200} and P_{300}), which originate largely from secondary and association cortices, were reduced in amplitude compared to what it was in hearing loss and age-matched controls. This could point to increased spontaneous activity in those areas so that stimulus-evoked activity can recruit fewer non-refractory neurons. Weisz et al. (2005b) compared individuals with tinnitus with controls and used tonal edge-frequency stimuli and tonal stimuli with a frequency one-octave below the edge. They found that the N_{100} dipole strength for individuals with tinnitus and controls was not different for edge-frequency tones but that the N_{100} responses were significantly larger for tonal stimuli with one-octave below the edge-frequency in the right hemisphere of the individuals with tinnitus. The source location for the edge-frequency dipole was abnormal, but in contrast to the Mühlnickel et al. (1998) findings, the deviation from the control position was not related to tinnitus distress. This suggests that map changes in itself cannot explain the strength of the tinnitus percept. The data from Weisz et al. (2005b) do suggest increased neural synchrony (larger N_{100}), in contrast to the interpretation of the Attias et al. (1993) data, and enhanced right hemisphere activity as in the PET findings of Reyes et al. (2002) and Mirz et al. (1999). The differential hemispheric activity, with the strongest activity unrelated to the side of tinnitus is not explained by any bottom-up modeling of tinnitus (Eggermont and Roberts, 2004) and does suggest mechanisms potentially related to the differential representation of fast periodic (left hemisphere) vs. slow modulated or continuous

(right hemisphere) sounds (Zatorre and Belin, 2001).

Gerken et al. (2001) did not find differences in the auditory brainstem response (ABR), except for the latency of wave VII, but they did observe exceptionally large amplitude of the MLR in their “problem tinnitus” group compared to a hearing loss group without tinnitus and an elderly group (where also large MLRs were found but not as consistent as in the tinnitus group). This could point to either increased neural synchrony, reduced central inhibition a known aspect of aging (Willott et al., 1997), or both.

Single unit recording in humans

Tinnitus can be considered as a positive symptom disorder characterized by “neuronal hyperactivity due to loss of afferent inhibition”, and has been linked to bursting neural activity in the medial thalamus. In one study, over 2000 single units (SUs) were recorded in the medial thalamus prior to medial thalamotomy in 104 patients, 6 of which had tinnitus. Approximately 99% of the 2000 SUs were unresponsive to sensory stimulation or motor activation, while 41% of the total showed rhythmic (at ~4 Hz) or random burst-firing typical for low-threshold calcium spike bursts (Jeanmonod et al., 1996). These authors suggested a linkage between some forms of tinnitus and EEG spindling which is initiated by rhythmic bursting in the thalamus.

Otoacoustic emissions in humans

Spontaneous otoacoustic emissions are low-level sounds emitted by the healthy normal ear (outer hair cells) that are recordable with sensitive microphones inserted in the ear canal. In ~6–12% (or at least 4% according to Penner and Jastreboff, 1996) of normal hearing persons spontaneous otoacoustic emissions are considered at least partially responsible for the tinnitus (Norton et al., 1990; Penner, 1990). Plinkert et al. (1990), elaborating on a proposal by Kemp (1981), speculated that the pathological long-term movements of a small local group of not more than 60 affected

outer hair cells may account for tonal tinnitus. In most cases, however, spontaneous otoacoustic emissions and tinnitus are independent phenomena (Wilson and Sutton, 1981; Penner and Burns, 1987; Penner, 1992). Although spontaneous emissions could theoretically produce increased “spontaneous firing” in neurons innervating the basilar membrane at the emission site, central nervous system adaptation may preclude their audibility. Occasionally, however, some individuals have been reported to hear intermittent spontaneous otoacoustic emissions as intermittent tinnitus (Burns and Keefe, 1992).

In a patient with an overdose of salicylate, transient evoked otoacoustic emissions (TEOAE) were absent and distortion product otoacoustic emissions (DPOAE) were reduced but still present despite a 50 dB hearing loss, but the input-output functions were linearized suggesting a loss of outer hair cell functioning (Janssen et al., 2000). In individuals with tinnitus with normal hearing, DPOAE amplitudes were also reduced compared to normal hearing controls (Ozimek et al., 2006). Twenty-four hours after involuntary noise trauma in military personnel, TEOAE amplitudes were reduced when the tinnitus appeared to be long lasting and were a better predictor for persisting tinnitus than just the amount of hearing loss (Nottet et al., 2006). In contrast, in tinnitus resulting from head trauma in individuals with normal audiograms, the TEOAE amplitudes were increased, the incidence of spontaneous acoustic emission was doubled, and contralateral tinnitus suppression was reduced, all pointing to a potential deficit in the medial olivocochlear bundle activity (Ceranica et al., 1998). Thus, otoacoustic emissions are useful in the delineation of some mechanisms involved in cochlear functioning that might accompany tinnitus, but they do not generally relate to tinnitus itself.

Multi-modal effects in humans

Head and neck injuries are a profound cause of tinnitus, and in addition head and neck contractions can also modulate existing tinnitus in 80% of patients. More importantly in 60% of patients

with no tinnitus at the time of testing such contractions could induce tinnitus even in the profoundly deaf (Levine et al., 2003). Møller et al. (1992) showed that median nerve stimulation could modulate existing tinnitus in 40% of ears, and Rubinstein (1993) showed that 33% of tinnitus patients could modulate their tinnitus with jaw movements. This suggests an important multi-modal aspect in the perception of tinnitus and points to different anatomical structures along the extra-lemniscal (non-classical pathways, see chapter 1) pathways, such as the external nucleus and cortex of the IC, and including the dorsal cochlear nucleus (DCN) as important ignition sites in the generation of tinnitus.

Neural correlates suggested by the human studies

Studies in humans have shown abnormalities such as elevated delta waves in the spontaneous spectrum of the EEG or MEG, relatively enhanced activation in the right hemisphere, increased evoked-potential or evoked-magnetic field amplitude, tonotopic map changes in AC, structural changes in the right-sided thalamus and increased SFRs in the IC. Head trauma induced tinnitus may differ from that induced by noise trauma and the former may have a peripheral component. Multi-modal effects suggest involvement of the extra-lemniscal pathway, pointing to DCN, the external nucleus of the IC (ICx) and secondary auditory cortex (AII) as important potential ignition sites for tinnitus.

Tinnitus inducing agents: etiology

Causes of tinnitus in humans can be catalogued on basis of epidemiological and clinical studies. Henry et al. (2005) list overviews from several studies suggesting that noise trauma is the single most unique cause of tinnitus (18%), followed by head and neck trauma (8%) and ear, nose and throat (ENT) infections and illnesses (8%), whereas drugs only account for 2% of known incidents of tinnitus.

Tinnitus is thus often related to hearing loss resulting from external causes such as noise

trauma and ototoxic drugs, potentially exacerbated by aging. Head and neck trauma causes tinnitus likely by increasing or modulating neural activity in the extra-lemniscal auditory pathways via the effect of trigeminal nerve activity on the DCN (Itoh et al., 1987; Shore et al., 2000). Individuals with vestibular schwannoma almost always have tinnitus and tinnitus is one of the three signs that define Ménière's disease.

Exposure to noise is commonly used in animal experiments for causing tinnitus, together with ototoxic drugs, among those most often salicylate. We will also include in our review the effects of cochlear ablation (as a method to induce profound hearing loss) and aging on the auditory system.

Putative neural correlates of tinnitus

The human studies reviewed above suggest changes in SFR (DCN and IC) and in neural synchrony (PAC) as correlates for tinnitus. Increased neural synchrony will be reflected in increased evoked potentials (or local field potentials, LFPs) as well as increased correlation in spiking times between simultaneously recorded neurons. Potentially other abnormalities in spontaneous firing such as increased burst firing cannot be excluded at this point. Another potential correlate of MEG studies suggested are changes in the cortical tonotopic maps.

Morphological and anatomical correlates of noise trauma

Exposure of chinchillas with a one-octave band of noise centered around 4 kHz and presented for 105 min at 108 dB sound pressure level (SPL) showed axonal degeneration in the DCN that peaked at 16 days post trauma (Bilak et al., 1996; Morest et al., 1998). However, in the auditory nerve (AN) and ventral cochlear nucleus (VCN) axonal degeneration continued for up to 8 months. This degeneration process was accompanied by an increase in small-diameter axons by up to 90% at 8 months post exposure (Bilak et al., 1996; Morest et al., 1998). In the posterior VCN (PVCN) there was a process of ongoing degeneration of synaptic

endings that seemed to continue for an indefinite period after the trauma suggesting that noise-induced hearing loss behaved similar to a neurodegenerative disorder of the auditory nervous system (Kim et al., 2004b). This neurodegeneration was accompanied by newly formed synapses on globular bushy cells, likely arising from central interneurons and thus signs of reorganization (Kim et al., 2004c). The regrowth of axons and terminals occurred over 24–32 weeks after exposure in such a way that the number of excitatory endings was fully restored but the number of inhibitory ones was only partly restored. Following trauma there is thus a loss and subsequent regrowth of synaptic endings with a reorganization of synaptic connections that favors excitation (Kim et al., 2004a). This imbalance in excitatory and inhibitory synapses could be the structural basis for the decline in inhibitory transmission in the VCN, and providing that the same mechanism is at work in DCN, potentially leading to an increase in neural discharge rate observed after noise-induced hearing loss.

Noise exposure that resulted in ~50 dB hearing loss across the entire frequency range also showed significant reduction in cell density in all subdivisions of the MGB and in layers IV–VI of the PAC in mice (Basta et al., 2005).

Pathophysiology: from ion channel to global brain changes

Ion channels

The inner hair cells in the cochlea are equipped with only one type of Ca^{2+} channels, namely the L-type. These calcium channels regulate the release of glutamate from the inner hair cells. Blocking these L-type channels with nimodipine results in a decrease in spontaneous and stimulus-driven firing rates in AN fibers (Robertson and Paki, 2002). In the IC, salicylate appears to block this L-type Ca^{2+} channel (Liu et al., 2005). If salicylate would do the same in the inner hair cells, then one would expect a depression in compound action potential (CAP) amplitude regardless of stimulus level. This is not the case; only the low-intensity segment of

the input-output function is affected (Puel et al., 1990) and SFRs are reduced or unchanged following acute salicylate administration (Stypulkowski, 1990; Müller et al., 2003). The low-intensity effect on the input-output function points to an action of salicylate on the outer hair cell mediated cochlear amplifier (Tunstall et al., 1995; Kakehata and Santos-Sacchi, 1996; Lue and Brownell, 1999).

In the IC, the current through the L-type channels does not directly trigger neurotransmitter release but contributes, among others, to GABAergic transmission by activating the second messenger system and/or by increasing the intracellular calcium concentration (Liu et al., 2005). Salicylate blocks these L-type Ca^{2+} channels at levels close to 1 mM that are similar to the plasma levels in humans that result in tinnitus. Salicylate also blocks the outward and delayed rectifier K^{+} channels in rat IC, hence a decreased GABAergic transmission could result in neuron depolarization as well as increases in firing rate (Liu and Li, 2004).

Quinine is a K^{+} channel blocker, and results in broadening of the action potential (Lin et al., 1998), which could result in enhanced transmitter release, and thus likely increased SFR. However, the concurrent increase in the refractory period in AN fibers appears to offset this action (Mulheran, 1999). At higher dose quinine also blocks the Na^{+} current, which may cause the often-observed threshold increase. Quinine does not affect Ca^{2+} currents, but blocks Ca^{2+} activated K^{+} currents. The observed threshold increase could, just as after noise trauma, start loss of inhibition and central unmasking.

Lidocain, that can relieve tinnitus temporarily, blocks the fast voltage sensitive Na^{+} channels, but also two voltage-gated K^{+} channels (Kv3 and Kv1) that are present in anterior VCN (AVCN) bushy cells and medial nucleus of the trapezoid body (MNTB) principal cells. However, the reversible inhibition of the K^{+} channels does not occur at clinically relevant concentrations. Therefore these K^{+} channels are likely not involved in tinnitus generation (Trellakis et al., 2006). Peripheral fast voltage sensitive Na^{+} channels are likely not involved either since tinnitus could be suppressed with Lidocain in patients with sectioned

AN after vestibular schwannoma removal (Baguley et al., 2005). That means the suppressive effect is most likely to occur at more central levels than the brainstem.

Receptor systems

AMPA

Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) is the dominant glutamate receptor in the AN endings below the inner hair cells (Puel, 1995) (see also Chapter 12). AMPA receptors mediate the excitotoxic effect of excessive noise trauma leading to excessive amounts of glutamate in the synaptic cleft and resulting in neurite loss (Puel et al., 1998).

The first effect of unilateral cochlear ablation is AN fiber degeneration accompanied by deficient release and uptake of glutamate in the ipsilateral VCN (Potashner et al., 1997). After some time the residual release and uptake increases suggesting recovery of glutamatergic transmission. This effect was similar in the contralateral VCN suggesting a plastic change driven by signals from the ipsilateral VCN. Increased glutamatergic transmission was also seen in the superior olivary complex (SOC; Potashner et al., 1997; Suneja et al., 2000). The same phenomena were observed after unilateral noise trauma (see structural changes) and there was initially (in the 1st post-trauma week) increased release and depressed uptake, whereas by 14 days post trauma both release and uptake were down (Muly et al., 2004). However, after 90 days post trauma a resurgence of transmitter release coupled to an elevation of AMPA binding was noted, suggesting transmitter upregulation through plastic changes (Muly et al., 2004).

NMDA

Salicylate amplifies cochlear *N*-methyl-D-aspartic acid (NMDA)-mediated responses but has little or no effect on AMPA- and kainite-mediated responses (Peng et al., 2003). NMDA antagonists protect sensory hair cells from aminoglycoside ototoxicity (Basile et al., 1996) and can prevent

excitotoxicity induced by acoustic trauma (Duan et al., 2000). During 4 days of daily 300 mg/kg injections of salicylate, hearing loss reached 40 dB and DPOEAs dropped to noise levels, but completely recovered 1 day after the final dose (Guitton et al., 2003). Behavioral effects of tinnitus induced by salicylate, but not the resulting hearing loss, were abolished by NMDA receptor (NMDAR) antagonists. Tinnitus-like behavior could be induced by NMDAR agonists (Guitton et al., 2003). This suggests that inhibition of cycloxygenase by salicylate may be one of the mechanisms responsible for generation of tinnitus via activation of NMDARs. At birth, NMDARs are mainly comprised of the NR2B subunit in the cerebral cortex. Over the course of postnatal development, this is progressively replaced or augmented by the NR2A subunit. Twenty-four hours after a 3 h period of noise trauma the level of NR2A protein was significantly increased but at 72 h, the level of NR2A protein was back to normal levels (Wang et al., 2005).

GABA

Age-related changes in the central nucleus of the IC (ICC) include decrease in the number of gamma amino butyric acid (GABA)-immunoreactive neurons, decreased concentrations of GABA, decreases in GABA release, decreased glutamic acid decarboxylase (GAD) activity (the rate-limiting enzyme in the formation of GABA), decreased GABA_B receptor binding and a decreased number of presynaptic GABA releasing terminals. In addition a subtle effect on GABA_A receptors and no change in binding but increased sensitivity, was noted (Raza et al., 1994; Caspary et al., 1995; Milbrandt et al., 1996, 1997; Caspary et al., 1999). In PAC, significant decreases in GAD with age were found in layers II–VI, with the largest effects in layer II (Ling et al., 2005). Following noise trauma, significant decreases in GAD in IC were found in the first 42 h after the trauma, and complete recovery occurred after 30 days (Abbott et al., 1999; Milbrandt et al., 2000). After unilateral cochlear ablation, deficient GABA release in the ICC was found prior to 59 days post ablation,

but this was established back to control levels at 145 days post ablation, concurrent with the up-regulation of glutamate release in the same structure (Suneja et al., 1998b).

Glycine

Age-related changes include significant decrease in glycine receptor sites in rat AVCN and DCN (Milbrandt and Caspary, 1995). In old C57 mice (which exhibit progressive cochlear pathology with age) but not in middle age C57 and old CBA mice, the number of glycine receptors decreased significantly in DCN, suggesting that it is not only age that determines downregulation of glycine but also the amount of hearing loss (Willott et al., 1997). After unilateral cochlear ablation, a persistent deficiency in the glycinergic binding was found on the ablated side in VCN and lateral superior olive (LSO). The LSO on the intact side showed strengthened inhibition as binding was elevated and uptake near normal (Suneja et al., 1998a, b; Potashner et al., 2000).

ACh

Acetylcholine receptors (AChR) come in two flavors: muscarinic (mAChR) and nicotinic (nAChR). nAChR subunits $\alpha 9$ and $\alpha 10$ are located on the cochlear hair cells and mediate the medial efferent olivocochlear bundle response. These nAChR's are ligand-mediated ion channels that span the width of the membrane (Gomez-Casati et al., 2005; Lustig, 2006). In aging rats, the amount of cholineacetyl transferase (ChAT), an enzyme involved in the production of ACh, decreases by 22% in the ICc, by 56% in the nucleus of the lateral lemniscus (NLL) and is not affected in the cochlear nucleus (CN) (Raza et al., 1994). After unilateral cochlear ablation, mAChR binding becomes progressively larger over a 2-month period in VCN and in the corresponding granular layers, and DCN fusiform and deep layers (Jin and Godfrey, 2006) potentially reflecting receptor plasticity following loss of AN fiber innervation. After noise trauma, ChAT increased by 74% in ipsilateral AVCN and by 55–74% in ipsilateral DCN at

8 days post trauma. By 2 months post trauma, the level was still increased by 53% in the deep layers of the DCN on the exposed side (Jin et al., 2006). In rat DCN, intense noise exposure resulted in an upregulation of cholinergic receptors likely in the superficial layers, resulting in enhanced suppression of fusiform cell activity after application of carbachol (Kaltenbach and Zhang, 2007). The muscarinic antagonist scopolamine suppressed the expression of c-fos and arg3.1 in AC (Wallhäusser-Franke et al., 2006).

Vanilloid (VR1)

The vanilloid capsaicin receptor is co-localized with substance P in sensory fibers of the trigeminal ganglion innervating cochlear arteries (Vass et al., 2004). The vanilloid receptor (VR1) is also expressed in inner ear ganglion cells and activation thereof may contribute to hypersensitivity of these cells. During inflammatory processes or during cyclooxygenase inhibition (by salicylate) this could be an intrinsic source of activation of the spiral ganglion (Balaban et al., 2003) and, e.g., give rise to tinnitus.

5-HT

Serotonergic activity has been shown to increase the perception of chronic pain and phantom limb pain and thus may play a role in the perception of tinnitus (Simpson and Davies, 2000). Indeed, the serotonin receptor 5-HT_{2C} agonist 1-(3-chlorophenyl)piperazine (mCPP) increases anxiety in humans and animals and exacerbates the behavioral perception of salicylate-induced tinnitus (Guitton et al., 2005). Animals with knock-outs of this receptor show increased audiogenic seizure susceptibility (Simpson and Davies, 2000). Salicylate by itself increases the serotonergic activity in the rat for up to 6 h post injection in IC and PAC (Liu et al., 2003).

Single unit firing correlates

A generally accepted neural correlate of tinnitus is increased SFR. The SFR typically does not change with aging, neither in DCN fusiform cells (Caspary

et al., 2005) nor in DCN cartwheel cells (Caspary et al., 2006) or in layer V neurons of rat AC (Turner et al., 2005). After noise trauma, the SFR was significantly enhanced in vitro in chinchilla DCN fusiform cells (Brozoski et al., 2002), but not in rat DCN fusiform and cartwheel cells (Chang et al., 2002). In vivo experiments in hamster DCN indicate massive increases in SFR 5–180 days after noise exposure but not at 2 days (Kaltenbach et al., 2000). Complete or nearly complete transections of descending inputs did not affect significantly the magnitude of DCN hyperactivity (Zhang et al., 2006). This SFR increase correlated significantly with the strength of the behavioral index of tinnitus (Kaltenbach et al., 2004). In IC of mice, noise trauma significantly increased SFR (Ma et al., 2006). In PAC, significant increase in SFR occurred after at least 2 h following the trauma, but not immediately (<15 min) following it, whereas significant increases in neural synchrony did occur at that time (Noreña and Eggermont, 2003). The synchrony changes were restricted to the CF region above the trauma tone frequency. At least 3 weeks after the trauma, the SFR and neural synchrony were significantly larger than in controls at all CFs tested, so not only in the region of the hearing loss although that region showed more pronounced changes (Seki and Eggermont, 2003). About 1 month after daily cisplatin application, increased SFRs in the DCN of hamsters were found when there was severe outer hair cell loss, and slightly less so when this was accompanied by inner hair cell loss. No effect was found in the absence of or only minor outer hair cell loss (Kaltenbach et al., 2002; Rachel et al., 2002).

Chronic salicylate application in doses that did not produce auditory threshold increases did increase the compound spontaneous activity of the AN as measured at the round window (Cazals et al., 1998). Such levels can result in tinnitus without appreciable threshold increase (Bauer et al., 2000). Salicylate doses of 200 mg/kg failed to increase SFR in cat (Stypulkowski, 1990) and gerbil AN fibers (Müller et al., 2003), whereas a high dose of 400 mg/kg did (Evans et al., 1981; Eggermont, 1992). This high dose has potential systemic toxic effects, as cats do not metabolize salicylates. In rats, a high dose of 450 mg/kg

resulted in decreased mean interspike intervals (ISIs; suggestive for increased SFR) in ICc neurons (Jastreboff and Sasaki, 1986), and a lower dose (233 mg/kg) did the same for neurons in the ICx (Chen and Jastreboff, 1995). In the IC of guinea pigs, 200 mg/kg sodium salicylate increases mean SFRs from ~5 sp/s to ~19 sp/s at 100 min after application, firing rates then declined to baseline after 10 h. In control animals (saline infusion) the firing rate did not change significantly (Manabe et al., 1997). In mice, a dose of 200–300 mg/kg decreased SFR significantly in ICc (Ma et al., 2006). In cat AC, salicylate at a dose of 200 mg/kg did produce increased SFRs for high characteristic frequencies (CFs) in AII, and decreased SFRs in AI and anterior auditory field (AAF) for all CFs (Eggermont and Kenmochi, 1998). In awake rats, salicylate levels of 150 mg/kg that induced behavioral signs of tinnitus, decreased SFRs in AC significantly from 22 sp/s to 14 sp/s (Yang et al., 2007). In guinea pig AN, 10–30 mg/kg of quinine reduced the SFR significantly, increased the CF thresholds but did not change frequency-tuning curve bandwidth (Mulheran, 1999). Quinine administered at 200 mg/kg in cat increased SFRs in AII but not in AI and AAF (Eggermont and Kenmochi, 1998) and also increased neural synchrony at a dose of 200 mg/kg but not at half the dose (Ochi and Eggermont, 1997).

Population neural activity

Despite a reduction in the CAP of the AN and the LFP in the CN following noise trauma, the LFP in the IC was typically enhanced at high-intensity levels (Salvi et al., 1990, 2000; Wang et al., 2002). After salicylate application SU firing rates in AC of awake rats were reduced, but the LFP was enhanced at 5, 8 and 16 kHz (Yang et al., 2007) suggesting increased neural synchrony or reduced lateral inhibition resulting in unmasking of new excitatory units.

Global brain activation changes

Salicylate application reduced especially the high-frequency area uptake of 2-deoxyglucose (2-DG)

in IC of gerbils and activated high-frequency regions in AC (Wallhäusser-Franke et al., 1996). Twelve to 31 days after noise exposure, significant decreases in 2-DG uptake were found in the ipsilateral AVCN and PVCN, with respect to the exposed left ears. Exposed animals showed significant increases in 2-DG uptake in the ipsilateral NLL, ICc and MGB. No significant changes in uptake were observed in the ipsilateral DCN, SOC, AC and any contralateral structures (Zhang et al., 2003). One week after exposure to a high frequency (15–20 kHz noise band) 2-DG uptake in quiet, resulted in a decreased activity for the region with CFs above 30 kHz in the AVCN, DCN and ICc. Cutting the dorsal acoustic striae caused the uptake to decrease in ICc, suggesting that the CN is the major contributor to spontaneous activity in ICc (Imig and Durham, 2005). The early gene transcription factor c-fos expression was not enhanced in the auditory brainstem after salicylate application (Wallhäusser-Franke, 1997) but did increase in the AC. Impulse noise also caused expression in the DCN as well as in AC (Wallhäusser-Franke et al., 2003).

Summary of pathophysiology by tinnitus-inducing agent

I will now summarize the pathophysiology induced by some important tinnitus-inducing agents (Table 1).

Salicylate

Chronic salicylate can result in tinnitus without threshold increase and increases the compound SFR of the AN as measured at the round window. High dose salicylate blocks L-type Ca^{2+} channels in the IC, but not in inner hair cells, at levels that in humans result in tinnitus. Salicylate shuts down the outer hair cell mediated cochlear amplifier, amplifies cochlear NMDA mediated AN responses but has little or no effect on AMPA- and kainite-mediated AN responses. Acute and relatively high doses of salicylate reduce the SFR in ANF or leave them unchanged. In rat ICx the SFR increased, in

Table 1. Changes in ion channel, receptor systems, single cell and population activity (See Color Plate 2.1 in color plate section.)

	OHC	ANF	CN	IC	MGB	AC
K^+				↓		
Ca^{2+}				↓		
AMPA		≈	↓ → ↑			
NMDA		↑	↓ → ↑			↑ → ↓
Glycine			↓ ↓			
GABA				↓ → ↑		↓
ACh			≈ =	↓		
Vanilloid	↑					
Serotonin				↑		↑
OAEs	↓					
SFR		(≈ ↓) ↓ ↓	≈ = ↑	↑ ↑		↑ ↑ ≈ ↑
AEPs				↑		↑ ↑
XCORR						≈ ↑ ↑
EEG/MEG						(↑ ↓)
2-DG				↑		↑
PET						↑
BOLD				↑		
MRI					↑	

Red: salicylate; Blue: noise trauma; Green: aging; Orange: cochlear ablation; Violet: quinine; Black: Cisplatin;

↓ → ↑: initially down then recovers; (↑ ↓): EEG delta up, alpha down; ≈: no change; (≈ ↑): acute no change, chronic up.

rat ICc the mean ISI decreased, which is suggestive of an SFR increase, whereas in mice ICc the SFR decreased significantly. In AC of awake rats, salicylate levels that induced behavioral signs of tinnitus, decreased SFR significantly, whereas the LFP was enhanced suggesting increased neural synchrony or reduced lateral inhibition. In anesthetized cat AC, salicylate produced increased SFRs for high CFs in AII, and decreased SFRs in PAC and AAF for all CFs. Salicylate application reduced especially the high-frequency area uptake of 2-DG in AVCN and DCN, and in the IC of gerbils but activated high-frequency regions in AC. The early gene transcription factor c-fos expression was not enhanced in the auditory brainstem after salicylate application but did increase in the AC.

The data on salicylate appear to reflect two different effects: increased SFR in rat ICx and cat AII, and decreased activity in mice (ICc), gerbils (CN, IC) and cats (PAC). This suggests a division between the lemniscal areas and the non-lemniscal

ones, but species differences and effects of anesthesia vs. awake cannot be excluded.

Noise trauma

Noise trauma shows axonal degeneration in the DCN that peaked at 2 weeks post trauma, whereas nerve degeneration in AN and in VCN continued for up to 8 months. Degeneration of synaptic endings and subsequent regrowth of synaptic endings with a reorganization of synaptic connections that favors excitation was found, and may be the substrate for increased SFR. More centrally there is also a significant reduction in cell density in all subdivisions of the MGB and in layers IV–VI of PAC. Significant decreases in GAD were found initially after the trauma, but complete recovery occurred after 1 month. ChAT increased in ipsilateral AVCN and DCN by 1-week post trauma, and was by 2 months post trauma still present in the deep layers of the DCN. In rat DCN, intense noise exposure resulted in an upregulation of cholinergic receptors in the superficial layers. After noise trauma, the SFR was significantly enhanced in vitro in chinchilla DCN fusiform cells, but not in rat DCN fusiform and cartwheel cells. In vivo experiments in hamster DCN indicate massive increases in SFR at least 5 days after noise exposure but not at 2 days. This SFR increase correlated significantly with the strength of the behavioral index of tinnitus. In IC of mice, noise trauma significantly increased SFR. In cat PAC, significant increase in SFR occurred after at least 2 h following the trauma, but not immediately (<15 min) following it, whereas significant increases in neural synchrony, restricted to the CF region above the trauma tone frequency, did occur immediately. At least 3 weeks after the trauma, the SFR and neural synchrony were significantly larger than in controls. Impulse noise also caused c-fos expression in the DCN as well as in AC. Despite a reduction in the CAP of the AN and the LFP in the CN following noise trauma, the LFP in the IC was typically enhanced at high-intensity levels pointing to increased synchrony or decreased inhibition.

The noise trauma results thus point to potential species differences at the level of the DCN, and to the potentially important role of neural synchrony. The long time delay for the SFR increase in the DCN, compared with the nearly immediate effect in AC suggests a large role for the descending auditory system.

Cochlear ablation

Cochlear ablation initially results in a deficient release and uptake of glutamate in the ipsilateral VCN and SOC concurrent with AN fiber degeneration but after some time glutamatergic transmission increases again. Deficient GABA release in ICc was found in the first 2 months post ablation, but this fully recovered at 4.5 months post-unilateral ablation, concurrent with the upregulation of glutamate release in the same structure. A persistent deficiency in the glycinergic binding was found on the ablated side in VCN and LSO. mAChR binding became progressively larger over a 2-month period in VCN and in the DCN granular layers, fusiform and deep layers potentially reflecting receptor plasticity. No effects of ablation on the SFR have been published.

Aging

Aging, likely in combination with hearing loss, significantly decreased glycine receptor sites in rat CN. In the ICc aging decreased the number of GABA-immunoreactive neurons, decreased concentrations of GABA, decreased GABA release, decreased GAD activity (the rate-limiting enzyme in the formation of GABA), decreased GABA_B receptor binding and decreased the number of presynaptic GABA releasing terminals. In PAC, significant decreases in GAD with age were found in layers II–VI, with the largest effects in layer II. In aging rats, the amount of ChAT decreased in the ICc, and in NLL but not in the CN. The SFR typically does not change with aging. So although aging will exacerbate any existing tinnitus, due to its downregulation of inhibition, it does not produce tinnitus on its own.

Tonotopic map changes

Local mechanical damage to the cochlea (Robertson and Irvine, 1989; Rajan et al., 1993), ototoxic damage to the cochlea (Harrison et al., 1991), and noise-induced hearing loss all cause tonotopic map changes in PAC (Eggermont and Komiya, 2000; Seki and Eggermont, 2002; Noreña et al., 2003). The map changes are not causally related to the hearing loss (Noreña and Eggermont, 2005) and can occur in the absence of hearing loss as measured by ABR (Noreña et al., 2006) but are always accompanied by increased SFR and increased neural synchrony (Noreña and Eggermont, 2003; Seki and Eggermont, 2003; Noreña and Eggermont, 2005, 2006).

Map changes do not occur if immediately after noise trauma a compensatory complex sound that mimics in bandwidth and level the expected hearing loss is presented for several weeks (Noreña and Eggermont, 2005). When this happens, the downregulation of inhibition that usually follows noise-induced hearing loss likely does not occur and the unmasking of new excitatory inputs (Noreña et al., 2003) does not happen or is reversed. When this ‘unmasking’ trigger for tonotopic map reorganization is absent, map changes do not occur, despite a remaining hearing loss.

Tonotopic map changes can occur in the absence of peripheral hearing loss, for instance, following a long and continuous presentation of a 5–20 kHz multi-frequency sound (Noreña et al., 2006). This sound exposure, potentially by depressing the central synapses of the lemniscal pathway in thalamus and cortex, creates a functional lesion that is very similar to that of a restricted cochlear lesion. For instance, the SFR and neural synchrony do increase significantly compared to normal hearing controls and consequently one could speculate that this constitutes a model of tinnitus in the absence of a measurable hearing loss.

Weisz et al. (2005b) compared human individuals with tinnitus with normal controls and used tonal edge-frequency stimuli and tonal stimuli with one-octave-lower frequency to elicit evoked magnetic fields. They found that the source location for the edge-frequency N_{100} dipole was abnormal, in line with earlier findings by

Mühlnickel et al. (1998). However, the map abnormalities in the Weisz et al. (2005b) study did not relate to the strength of the tinnitus percept, whereas it did in the N_{100} studies by Mühlnickel et al. (1998) and the SSR by Diesch et al. (2004). This suggests that tonotopic map changes might be an epiphenomenon resulting largely from the downregulation of inhibition and the subsequent unmasking of new excitatory activity that also gives rise to increased SFR and increased neural synchrony. Preventing the downregulation of central inhibition may be the key point of attack.

What is the neural correlate of tinnitus?

In the bottom-up studies of tinnitus increased SFR and, to a lesser extent, neural synchrony have attracted most of the attention. It is doubtful whether increased SFRs in subcortical structures (DCN, IC) will lead to increased SFR in cortex. It is far more likely that increased neural synchrony in subcortical structures propagates along the auditory pathway (Kimpö et al., 2003) and ultimately result in increased synchrony and/or SFRs in cortex. Human studies using fMRI that find increased activation in certain brain regions suggest an increased SFR in those regions. Enlarged evoked potential or magnetic fields in contrast imply increased neural synchrony as its cause. The fMRI data of Melcher et al. (2000) point to increased SFR in IC, whereas evoked potential data (Wang et al., 2002) point to increased synchrony in that same structure. It is likely that both conditions co-occur as both result from down-regulated inhibition (Noreña and Eggermont, 2005, 2006).

EEG and PET data (Mirz et al., 1999; Reyes et al., 2002; Weisz et al., 2005a) suggest that a pronounced stronger activity over the right hemisphere correlates with tinnitus strength. The character of tinnitus may match with the known hemispheric specialization that assigns the left to rapid temporal processing and the right to slow spectral processing (Zatorre and Belin, 2001). But there is a difference between right hemisphere processing of tinnitus as a steady-state sound and signaling its loudness, than assuming that this is a neural correlate or a pathophysiological sign of tinnitus.

Abbreviations

AAF	anterior auditory field
ABR	auditory brainstem response
AC	auditory cortex
ACh	acetylcholine
AChR	acetylcholine receptor
AII	secondary auditory cortex
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AN	auditory nerve
AVCN	anterior ventral cochlear nucleus
BA	Brodman area
BOLD	brain oxygen level dependent
CAP	compound action potential
CF	characteristic frequency
ChAT	cholineacetyl transferase
CN	cochlear nucleus
DCN	dorsal cochlear nucleus
2-DG	2-deoxyglucose
DPOAE	distortion product otoacoustic emission
EEG	electro-encephalogram
ENT	ear, nose and throat
ERP	event-related potential
fMRI	functional magnetic resonance imaging
GABA	gamma amino butyric acid
GAD	glutamic acid decarboxylase
5-HT	serotonin
IC	inferior colliculus
ICc	central nucleus of the IC
ICx	external nucleus of the IC
ISI	interspike interval
LFP	local field potential
LSO	lateral superior olive
mCPP	1-(3-chlorophenyl)piperazine
MEG	magneto-encephalogram
MGB	medial geniculate body
MLR	middle latency response
MNTB	medial nucleus of the trapezoid body
NLL	nucleus of the lateral lemniscus
NMDA	<i>N</i> -methyl-D-aspartic acid
NMDAR	NMDA receptor
PAC	primary auditory cortex
PET	positron emission tomography

PVCN	posterior ventral cochlear nucleus
rCBF	regional cerebral blood flow
SFR	spontaneous firing rate
SOC	superior olivary complex
SPL	sound pressure level
SSR	steady-state response
SU	single unit
TEOAE	transient evoked otoacoustic emissions
VCN	ventral cochlear nucleus
VR1	vanilloid receptor

Acknowledgements

This study was supported by the Alberta Heritage Foundation for Medical Research, a Canadian Institutes of Health Research — NET grant, and the Campbell McLaurin Chair for Hearing Deficiencies.

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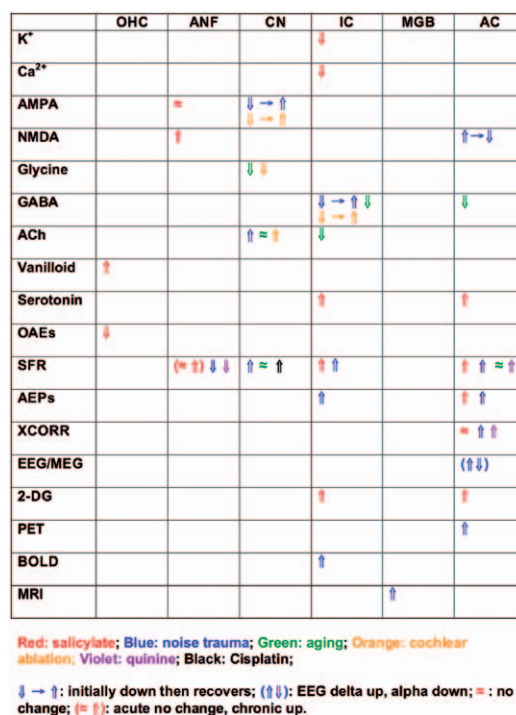


Plate 2.1. Changes in ion channel, receptor systems, single cell and population activity. (For B/W version, see page 28 in the volume.)

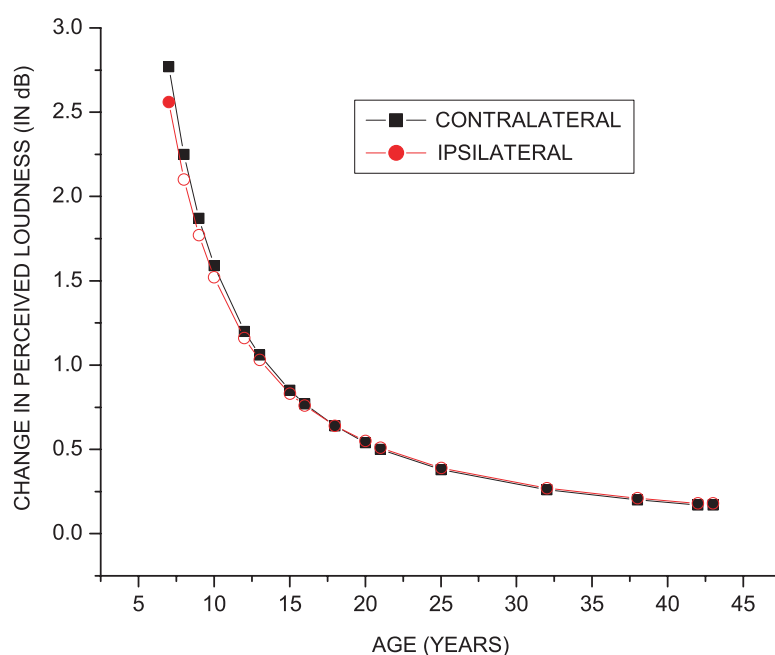


Plate 3.2. Average change in perceived loudness during median nerve stimulation, as a function of the participants' age. Adapted with permission by Elsevier, from Møller and Rollins (2002). (For B/W version, see page 42 in the volume.)

CHAPTER 3

The role of neural plasticity in tinnitus

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Abstract: There is considerable evidence that expression of neural plasticity plays a central role in the development of the abnormalities that cause many forms of tinnitus. Expression of neural plasticity can change the balance between excitation and inhibition, promote hyperactivity, and cause re-organization of specific parts of the nervous system or redirection of information to parts of the nervous system not normally involved in processing of sounds (such as the non-classical, or extralemniscal pathways). The strongest promoter of expression of neural plasticity is deprivation of input, which explains why tinnitus often occurs together with hearing loss or injury to the auditory nerve.

Keywords: tinnitus; neural plasticity; neuropathic pain

Introduction

There is considerable evidence that expression of neural plasticity can cause tinnitus, hyperacusis and affective disorders such as depression and phonophobia. Neural plasticity is a property of the nervous system that allows specific parts of the nervous system to change its function and its organization. Expression of neural plasticity can cause change of synaptic efficacy (Wall, 1977), creation or elimination of synapses, and elimination or creation of new connections through sprouting of axons and dendrites or elimination of axons and dendrites (Møller, 2006b). Plastic changes in the nervous system may also include change in protein synthesis in nerve cells (Sie and Rubel, 1992).

Change in synaptic efficacy in the form of unmasking of dormant (ineffective) synapses was shown to occur in the spinal cord in response to

deprivation of input (by severance of dorsal roots) (Wall, 1977) but expression of neural plasticity can also mask effective synapses so that they become ineffective. Change in protein synthesis in nerve cells in the cochlear nucleus has been shown to occur in response to severance of the auditory nerve (Sie and Rubel, 1992). Such changes may alter excitability and it may cause re-routing of information or re-mapping of nuclei in the cerebral cortex. Studies in animals have shown that deprivation of input lowers the threshold of stimulation of the auditory nervous system (Gerken et al., 1984) and changes its temporal integration (Gerken et al., 1991) thus a further example of how deprivation of input can cause expression of neural plasticity.

Most of our understanding of the role of neural plasticity in causing symptoms and signs of disorders (Møller, 2006b) comes from studies of neuropathic pain (Dubner and Basbaum, 1994; Doubell et al., 1999; Woolf and Salter, 2000) and there are considerable similarities between central neuropathic pain and tinnitus (see Chapters 4 and

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18). Evidence has been presented that symptoms of several other diseases can also be caused by expression of neural plasticity (Møller, 2006b) such as hemifacial spasm (HFS), and synkinesis after facial nerve injuries (Brach et al., 1997).

Change in protein synthesis and change in synaptic efficacy occurs within hours of being initiated by deprivation of input, whereas morphological changes such as elimination of synapses, axons or dendrites or creation of synapses, axons or dendrites takes much longer time. In fact, deprivation of input is probably the strongest factor for promoting expression of neural plasticity.

Loss of input to the auditory nervous system can have two kinds of effects both of which may promote tinnitus: Deprivation of auditory input can cause topographic map re-organization in cerebral cortices (Kaas, 1991; Kral et al., 2000) re-organization of the auditory cortices has been associated with tinnitus and it may be involved in abnormal perception of sound. The fact that tinnitus often is associated with hearing loss, especially high frequency hearing loss, supports the hypothesis that loss or reduction of input from the periphery can promote or initiate tinnitus. Overstimulation and trauma are other important factors but the cause of expression of neural plasticity from overstimulation is likely caused by the hearing loss that results from the overstimulation.

It has been shown that exposure to sounds may have beneficial effects by reducing hearing loss after noise trauma (Noreña and Eggermont, 2005). Animal experiments have shown that exposure to an “augmented acoustic environment” may slow the development of hearing loss (Turner and Willott, 1998; Willott et al., 2000).

It is a characteristic for expression of neural plasticity that the changes in function (even when morphological changes are involved) are not associated with any detectable morphological abnormalities using clinical imaging methods. However, the so-called functional imaging methods (fMRI, PET scans) have shown some ability to visualize changes in function that are associated with expression of neural plasticity. These methods have been used to study changes in the function of the auditory system that are associated with tinnitus (Talavage et al., 2000; Plewnia et al., 2007).

Three different kinds of abnormalities in the auditory system that are caused by expression of neural plasticity may be involved in causing severe tinnitus, namely changes that cause hyperactivity, re-organization (re-mapping) of neural structures, and re-routing of information. Hyperactivity may be caused by reduced inhibitory influence such as occur in connection with hearing loss of cochlear origin where input to the nervous system that is normally inhibitory is reduced. Re-routing and re-mapping may be caused by changes in synaptic efficacy, creation or elimination of synapses, axons or dendrites.

Expression of neural plasticity is often associated with effects that are beneficial such as re-organizing the nervous system after injuries, or by adapting the nervous system to changing demands such as for example occurs in connection with cochlear or cochlear nucleus implants (Kral and Tillein, 2006; Kral et al., 2006). However, the ability of sensory nervous systems to re-organize and change function can also cause symptoms and signs of disease, and expression of neural plasticity plays an important role in creating the symptoms and signs of many disorders (Møller, 2006b) including tinnitus (Møller, 2006a).

Deprivation of input may increase excitability in the cochlear nucleus, because some of the lost input normally had inhibitory influence on cochlear nucleus cells and it may promote expression of neural plasticity. Deprivation of input is a strong general promoter of expression of neural plasticity (Møller, 2006b).

There is also evidence that short-term re-organization may involve change in synaptic efficacy resulting in disinhibition of suppressed GABAergic inputs and potentiation of silent NMDA-mediated synapses (Jain et al., 1998), and change in protein synthesis (Sie and Rubel, 1992) while long-term re-organization is probably mostly mediated by dendritic and axonal sprouting, or elimination of axons, dendrites or synapses.

Activity may induce neural plasticity and such activity-induced expression of plasticity has been described as “neurons that fire together wire together,” an expression that is often referred to Hebb (1949). Although the exact statement is not

found in his writing, it very much represents his theories.

Many forms of tinnitus are caused by expression of neural plasticity going awry creating symptoms instead of adapting the nervous system to changing demands and restitution of lost function such as occurs after injuries (Møller, 2006b). Some forms of tinnitus are phantom phenomena with similarities to the phantom limb (Jastreboff, 1990). Phantom sensations such as those that occur in connection with amputated limbs (Melzack, 1992) are other examples of misdirected plastic changes. The phantom limb syndrome is a typical response to deprivation of input that may result in pain and tingling (Flor et al., 1995; Møller, 2006b).

Plastic changes in the central nervous system are responsible for some forms of pain such as central neuropathic pain (Devor, 1988; Møller, 2006b) (Chapter 4). In fact much of our understanding of how expression of neural plasticity can cause symptoms and signs of disorders (Møller, 2006b) comes from studies of neuropathic pain (Dubner and Basbaum, 1994; Doubell et al., 1999; Woolf and Salter, 2000).

While acute pain serves important functions central neuropathic pain does not seem to serve any beneficial function, neither does tinnitus.

Re-organization of the cerebral cortex

Cortical maps changes can occur as a result of expression of neural plasticity. It has been observed to occur in tinnitus (Mühlnickel et al., 1998) and indirectly evidence of re-organization comes from studies of the effect of electrical (Chapter 36) and magnetic stimulation of the auditory cortex (Chapters 34 and 35). Other studies have shown evidence of re-organization of the auditory cortex in response to sound stimulation (Kilgard and Merzenich, 1998). Re-organization of the somatosensory cortex in response to deprivation of input (amputation of a finger) has been shown many years ago by Merzenich and his colleagues (Jenkins et al., 1990).

Studies in humans have shown that the source of the N_{100} dipole in the evoked magnetic field in response to tonal edge-frequency stimuli in

individuals with tinnitus compared with that of normal controls was abnormal as was the response to tonal stimuli with one octave-lower frequency (Weisz et al., 2005b), confirming the results of other studies (Mühlnickel et al., 1998). However, the abnormalities in cortical mapping in the study by Weisz et al. (2005b) was not correlated to the strength of the tinnitus, as it did in the N_{100} studies by Mühlnickel et al. (1998) and the steady-state response by Diesch et al. (2004). This has been interpreted to indicate that the abnormalities in the tonotopic map in individuals with tinnitus may be an epiphenomenon that is caused by decreased inhibition causing unmasking of excitatory activity and possibly to increased spontaneous firing rate and increased neural synchrony.

Anatomical location of the physiological abnormality that causes tinnitus

The fact that a specific structure shows abnormal neural activity does not mean that the anatomical localization of the physiological abnormality is that structure. For example, abnormalities in the thalamic sensory nucleus can be reflected in the activity in the cortex. While there are signs that the cerebral cortex in individuals with tinnitus is re-organized, it is not known which populations of neurons in the cerebral cortex are affected.

Signs of cortical re-organization in individuals with central neuropathic pain does not prove that the anatomical location of the physiological anomaly that cause the pain is in the cerebral cortex — it could have been caused by re-organization in the thalamus and just relayed to the cortex through the thalamo-cortical connection. If the re-organization would be restricted to neurons that received input directly from the thalamus (layer IV neurons), the re-organization would most likely not be in the cortex but rather in the thalamus that provides the input to the cortex. This means that it would not be possible to alter the pathology by interventions that are directed to the cortex, unless these interventions (such as electrical stimulation) activate descending pathways to the thalamic nuclei. For pain the abnormalities seem to be in the thalamus rather than the cortex because deep

brain stimulation of the thalamus can relieve pain. The beneficial effect of cortical stimulation may be from activating thalamic nuclei through the cortico-thalamic tract. In fact it has been shown in mice that somatosensory cortex stimulation can activate inhibitory networks in the thalamic reticular nucleus (Zhang and Jones, 2004). That nucleus controls (modulates) neural traffic in the thalamus and to and from the thalamus (Møller, 2003; Brodal, 2004). Its influence is mainly inhibitory and since it projects back to the thalamus, it becomes a part of a feedback loop. The neurons in the reticular nucleus receive input from other parts of the CNS such as the reticular formation and are thus affected by wakefulness.

Re-routing of information

Some studies have shown evidence that re-routing of information has occurred in some individuals with tinnitus (Møller et al., 1992; Cacace et al., 1994). One kind of re-routing causes an abnormal cross-modal interaction making input from other sensory system modulate activity in the auditory system and there are signs that such cross modal interaction are associated with some forms of tinnitus and that it may promote development of tinnitus. These observations have been taken as an indication of an abnormal involvement of the non-classical (extralemniscal) auditory pathways.

Involvement of the non-classical auditory pathways in tinnitus

Auditory information can ascend from the ear towards the cerebral auditory and association cortices in two different pathways, one known as the classical or lemniscal pathway and one known as the non-classical or extralemniscal pathway (Chapter 1). The classical pathways are also known as the specific pathways because of the distinct responses and the precise tuning of auditory neurons and that pathway (slow and accurate) and the non-classical pathways are also known as the diffuse system that provide fast connection to many parts of the brain (fast and dirty) (Møller, 2003). The midbrain nucleus of the

classical pathways is the central nucleus of the inferior colliculus (ICC) while the external nucleus (ICX) and the dorsal cortex of the inferior colliculus (DC) are involved in the non-classical auditory pathways (Aitkin, 1986; Møller, 2003). While the classical sensory pathways use the ventral nuclei of the thalamus, the non-classical sensory pathways use dorsal and medial thalamic nuclei. The ventral nuclei of the thalamus project to primary sensory cortices while the neurons of the dorsal thalamic nuclei project to secondary cortices, thus bypassing the primary cortices. Cells in the dorsomedial nuclei of the thalamus also project to other parts of the CNS such as the lateral nucleus of the amygdala. This subcortical route to the amygdala is known as the “low route” to the amygdala (LeDoux, 1992) in comparison to the route to the amygdala through the classical pathways, known as the “high route” (Fig. 1).

Neurons in the nuclei and the cerebral cortices of the classical sensory pathways only respond to one modality, while neurons of the non-classical auditory pathways responds several modalities such as the somatosensory stimulation and stimulation of the visual system.

It has been known for many years that the dorsal and medial thalamic nuclei are involved in certain forms of pain (physiologic or central neuropathic pain) (Møller, 2006b) and more recent studies have shown indications of involvement of the dorsal and medial parts of the thalamus in some forms of severe tinnitus (Møller et al., 1992). These studies made use of the fact that the non-classical ascending auditory pathways receive input from other sensory systems. Since cross-modal interaction occurs in the non-classical pathways but not in the classical pathways it is a sign of involvement of the non-classical auditory pathway if for example the perception of sound changes when the median nerve is stimulated electrically (Møller et al., 1995).

The fact that the non-classical auditory pathways provide a subcortical connection from the dorsal thalamus to the lateral nucleus of the amygdala (LeDoux et al., 1984; LeDoux, 1992; Møller, 2006a) (Fig. 1) may explain why depression and phonophobia often occur together with tinnitus.

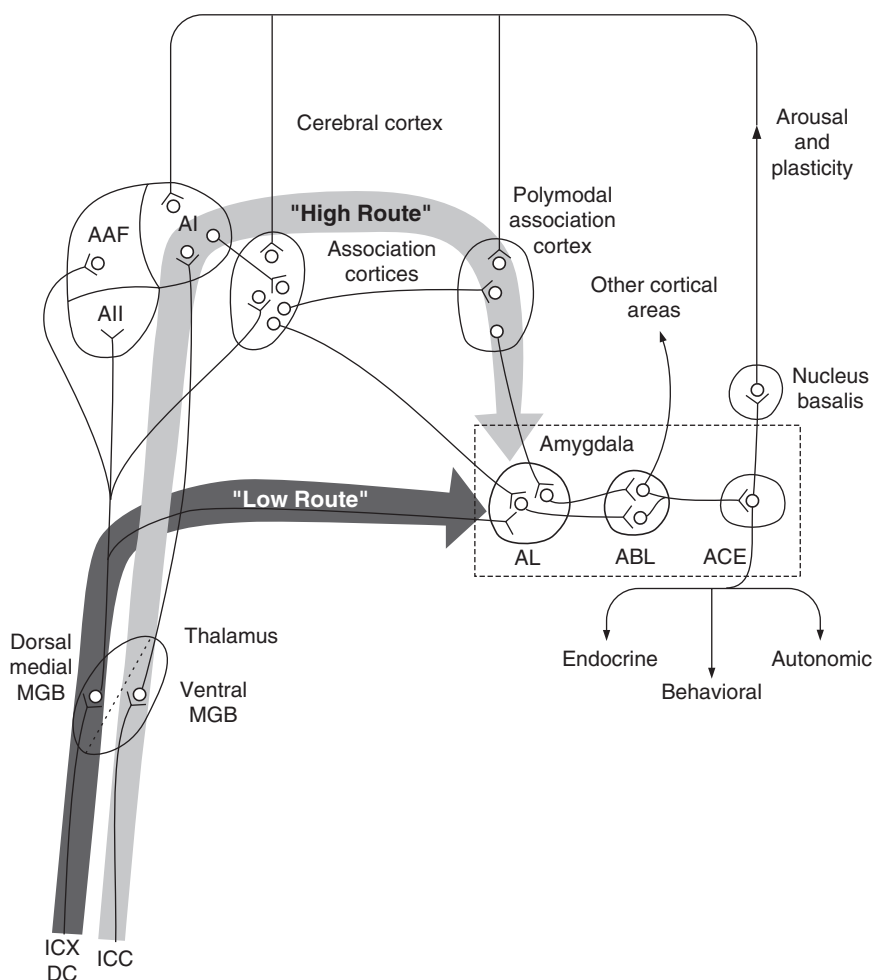


Fig. 1. Schematic drawing illustrating the "high route" and the "low route" from sensory systems to the lateral nucleus of the amygdala. Connections from the auditory nuclei in the thalamus to the lateral nucleus of the amygdala. AL: lateral nucleus of the amygdala; ABL: basolateral nucleus of the amygdala; ACE: central nucleus of the amygdala. Adapted with permission by Elsevier, from Møller (2003) after LeDoux (1992).

Temporomandibular joint (TMJ) problems are often associated with tinnitus (Morgan, 1992) and some individuals hear sounds when touching certain areas of the skin (Cacace et al., 1999). There are other signs that the somatosensory system is involved in tinnitus. The tinnitus of some individuals changes with changing gaze (Cacace et al., 1994), or is affected by contractions of their neck muscles (Levine, 1999). All these examples indicate involvement of the somatosensory system and thus possibly the existence of an abnormal involvement of the non-classical auditory

pathways that occurs because of expression of neural plasticity.

Studies of cross-modal interaction between the auditory and the somatosensory systems have shown signs of involvement of the non-classical pathways in hearing are found in children without known neurological disorders and it gradually decreases with age (Møller and Rollins, 2002) but it is rarely present in adults who do not have tinnitus (Møller et al., 1992). This indicates that maturation is associated with interrupting connections that have existed in early childhood. This

may occur by functionally masking of effective synapses that are ineffective in early life, or by eliminating synapses and dendrites anatomically. In individuals who do not have tinnitus, modulation of the loudness of sounds by electrical stimulation of the median nerve occurs rarely but it is a constant phenomenon in children, decreasing with age up to approximately 15 years (Møller and Rollins, 2002).

A study of 40 participants age 7–45 years without any known hearing problems (including tinnitus) were asked to detect changes in the loudness of sounds when the median nerve at the wrist was stimulated electrically (Møller and Rollins, 2002). The sounds were clicks generated by applying 20 μ s impulses to earphones, presented at a rate of 40 pulses per second (pps) at 65 dB above normal hearing threshold (HL). The electrical stimulation consisted of 100 μ s rectangular impulses presented at a rate of 4 pps through adhesive surface electrodes.

The change in loudness of the sound during median nerve stimulation was greatest in the youngest age group of the study (7–8 years)

(see Fig. 2). In this group of 10 participants, only 1 did not experience any noticeable change, 7 experienced an increase, and 2 experienced a decrease in loudness. In the age group of 13–19 years the experienced change was smaller (Fig. 2) and 3 of 10 participants did not experience any change in loudness during median nerve stimulation.

The conclusion of this study was that the non-classical auditory system is involved at least in loudness perception in children and that the involvement decreases with age, probably as a result of normal maturation of the auditory nervous system. It has been hypothesized (Møller and Rollins, 2002) that failure of this normal maturation process may cause some of the symptoms in children with developmental problems by maintaining the subcortical projection from the dorsal thalamus to the amygdala. A study indicates that the non-classical auditory pathways may be active in some individuals with autism (Møller et al., 2005).

Signs of involvement of the non-classical pathways in tinnitus were found in a study of 26

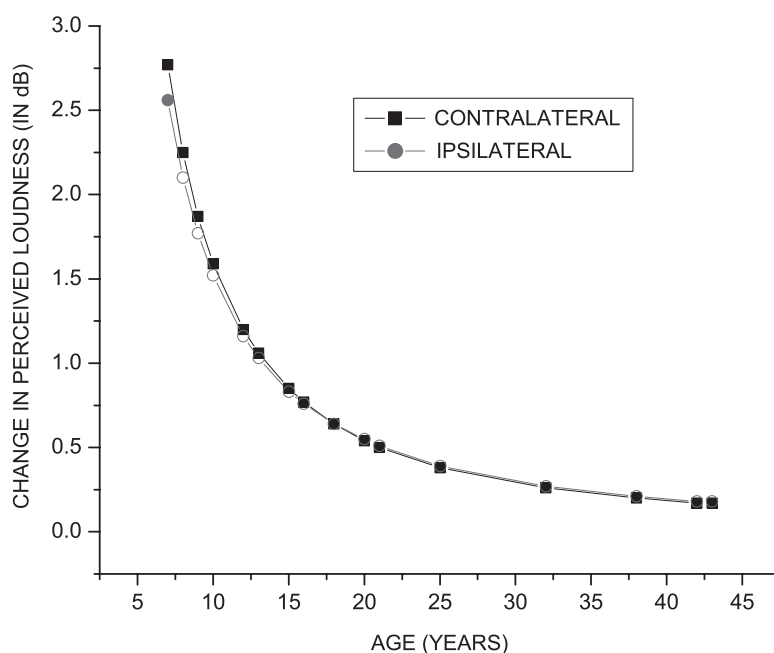


Fig. 2. Average change in perceived loudness during median nerve stimulation, as a function of the participants' age. Adapted with permission by Elsevier, from Møller and Rollins (2002). (See Color Plate 3.2 in the color plate section.)

individuals with tinnitus (14 severe, 5 moderate, and 7 mild). Median nerve stimulation caused an increase in the loudness of the tinnitus in 4 participants (2 severe, 1 moderate, and 1 mild tinnitus), a decrease in 6 participants (4 with severe, 1 moderate, and 1 mild tinnitus). Of the 16 participants, who had no noticeable change in loudness during median nerve stimulation, 8 had severe, 3 moderate, and 5 mild tinnitus, thus similar distribution as those who had signs of involvement of the non-classical pathways (Møller et al., 1992). The results of this study were interpreted to show that the non-classical pathways are rarely active in adults and that these pathways are active in some individuals with tinnitus.

Assuming that the reduction in the involvement of the non-classical pathways with age is a result of normal maturation processes, the signs that the non-classical pathways are active in autistic individuals support the hypothesis that failure of normal maturation causes some of the symptoms of autism.

In that respect it is interesting that children can have tinnitus (Chapter 15 and 16) and that they seem to perceive tinnitus differently than adults. Whether this has to do with the fact that the non-classical pathways are normally active in children is not known.

These processes of maturation involves expression of neural plasticity, and in particular, abnormalities such as those of autism may be regarded to be the result of some forms of neural plasticity not being activated or being activated incorrectly.

The effect of stimulation of the skin near the ear on tinnitus may be mediated by a different mechanism than that mediated by stimulating the skin on other parts of the body. The skin around the ear is innervated by fibers of the dorsal root of the C₂ vertebra and that segment of the spinal cord has connections to the DCN (Kanold and Young, 2001).

Neural plasticity and treatment

Activation of neural plasticity is in general use in treatment of traumatic brain injuries and injuries from strokes. It is also used for adaptation to

changed demands such as occurs in fitting of hearing aids and to an even greater extent in the use of cochlear and cochlear nucleus implants (Kral and Tillein, 2006). Activation of neural plasticity in such situations is done by training and it would also be expected that proper use of training also could reverse the changes caused by expression of neural plasticity that cause tinnitus. In fact several methods aimed at reversal of the plastic changes that cause tinnitus have been devised for that purpose and are in current use. One kind of treatment makes use of a combination of sound exposure and counseling. One of these methods, developed by Dr. Pawel Jastreboff is known as the tinnitus-retraining therapy (TRT) (Jastreboff and Jastreboff, 2000) (Chapter 40) and a similar form of treatment has been described by Richard Tyler (Chapter 41).

Even in individuals with tinnitus in whom there is a close contact between the auditory nerve and a blood vessel, the tinnitus that can be cured by the MVD operation may be caused by expression of neural plasticity. There are evidence from studies of another disorder, HFS, that MVD is beneficial because it reverses the plastic changes in the facial motonucleus that cause the symptoms of the disease (Møller, 1993). HFS is characterized by involuntary contractions of muscles on one side of the face and synkinesis is often present. There is evidence that these symptoms are caused by abnormal function of the facial motonucleus and that the changes in the function of the facial motonucleus are caused by expression of neural plasticity.

More recently, various kinds of stimulation of the auditory cortex such as through transcranial magnetic stimulation (TMS) (De Ridder et al., 2005; Kleinjung et al., 2005) (Chapters 34 and 35) or the direct electrical stimulation of the auditory cortex (De Ridder et al., 2006) (Chapter 36) have come to be in use for treating some forms of tinnitus. The prevailing hypothesis regarding the beneficial effect of such treatment is that it reverses changes in function most likely brought about by expression of neural plasticity (Mühlnickel et al., 1998). While the electrical or magnetic stimulation is aimed at the auditory cerebral cortices, it is possible that the beneficial effect is caused by an

action on the thalamic nuclei, which receive abundant input from the cerebral cortex through the cortico-thalamic tract (Møller, 2003). The thalamic nuclei have been the target for electrical stimulation (deep brain stimulation) for pain and in view of the similarities between pain and tinnitus (Chapter 4) a similar effect may be expected from electrical stimulation of the thalamus for these two disorders.

It is a general finding that it is easier to achieve a reversal of changes caused by expression of neural plasticity if done soon after that symptoms become manifest. That means that changes caused by expression of neural plasticity may become established with time and therefore more difficult to reverse.

Conclusion

There is considerable evidence that plastic changes in the CNS are implicated in generating the symptoms of many forms of tinnitus including hyperacusis and phonophobia that often accompany severe tinnitus. This evidence has opened many possibilities for treatment, some of which have already been explored and which are in clinical use.

Abbreviations

DC	dorsal cortex
DCN	dorsal cochlear nucleus
HFS	hemifacial spasm
ICC	central nucleus of the inferior colliculus
ICX	external nucleus
MVD	microvascular decompression
NMDA	<i>N</i> -methyl-D-aspartic acid
TMS	transcranial magnetic stimulation
TRT	tinnitus-retraining therapy

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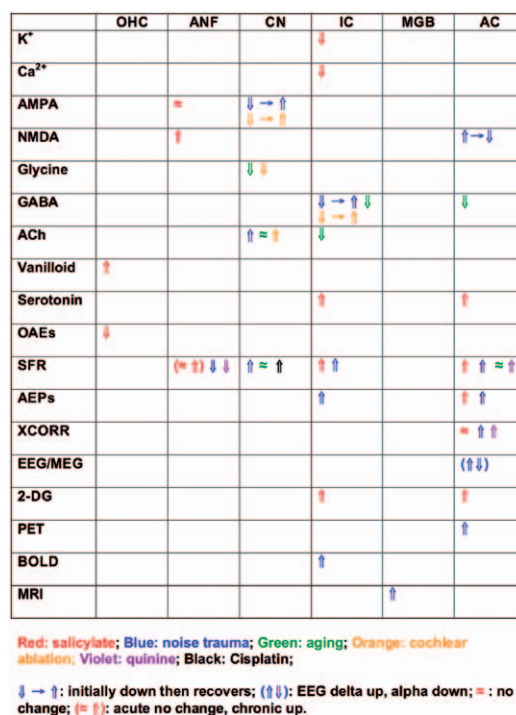


Plate 2.1. Changes in ion channel, receptor systems, single cell and population activity. (For B/W version, see page 28 in the volume.)

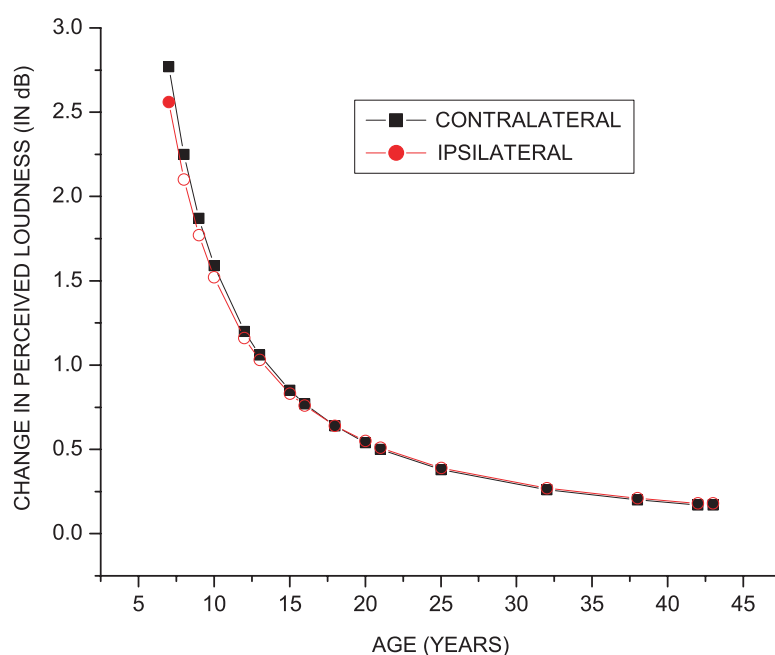


Plate 3.2. Average change in perceived loudness during median nerve stimulation, as a function of the participants' age. Adapted with permission by Elsevier, from Møller and Rollins (2002). (For B/W version, see page 42 in the volume.)

CHAPTER 4

Tinnitus and pain

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Abstract: Tinnitus has many similarities with the symptoms of neurological disorders such as paresthesia and central neuropathic pain. There is considerable evidence that the symptoms and signs of some forms of tinnitus and central neuropathic pain are caused by functional changes in specific parts of the central nervous system and that these changes are caused by expression of neural plasticity. The changes in the auditory nervous system that cause tinnitus and the changes in the somatosensory systems that cause central neuropathic pain may have been initiated from the periphery, i.e. the ear or the auditory nerve for tinnitus and receptors and peripheral nerves in the body for pain. In the chronic condition of tinnitus and pain, abnormalities in the periphery may no longer play a role in the pathology, but the tinnitus is still referred to the ear and central neuropathic pain is still referred to the location on the body of the original pathology. In this chapter we will discuss specific similarities between tinnitus and pain, and compare tinnitus with other phantom disorders. Since much more is known about pain than about tinnitus, it is valuable to take advantage of the knowledge about pain in efforts to understand the pathophysiology of tinnitus and find treatments for tinnitus.

Keywords: tinnitus; neural plasticity; neuropathic pain; phantom pain

Introduction

Many studies have shown that some forms of severe tinnitus have similarities with central neuropathic pain¹ (Tonndorf, 1987; Møller, 1997, 2000). (Central neuropathic pain is pain that occur without stimulation of pain receptors). Many forms of subjective tinnitus are phantom sensations that are symptoms of abnormalities rather than diseases. Absence of physical signs is a common characteristic of both tinnitus and central

neuropathic pain, and lack of objective tests that can detect and quantify the severity of these two conditions hamper treatment and individuals with these disorders are sometimes perceived as being exaggerating the severity of their symptoms.

Perception of sensory (and painful) stimuli is abnormal in many forms of tinnitus and central pain. Many individuals who have severe tinnitus often have hyperacusis² and individuals with central pain often have hyperpathia³.

Tonndorf (Tonndorf, 1987) found similarities between tinnitus and pain related to the gating

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¹The term "central neuropathic pain" means pain caused by abnormalities in the function of the nervous system that occur without input from the periphery.

²Hyperacusis is a lowered tolerance for sounds than normally.

³Hyperpathia is an explosive reaction to painful stimuli, thus a lower tolerance for painful stimuli and the perception of pain to such stimuli is prolonged.

theory of Melzack and Wall (1965). Shea et al. (1981) discussed similarities between tinnitus and pain in connection with the use of lidocaine or lidocaine-like drugs in the treatment of tinnitus.

Characteristics of tinnitus and central neuropathic pain

Studies have found that individuals with severe (central) pain have abnormal temporal integration of painful stimuli (Møller and Pinkerton, 1997; Maixner et al., 1998; Nie et al., 2006) (Fig. 1). Few studies have addressed temporal integration in individuals with tinnitus but animal experiments have shown altered temporal integration in the auditory nervous system after deprivation of auditory input (Gerken et al., 1991) and after overstimulation with sound (Szczepaniak and Møller, 1995; Kaltenbach, 2000), both of which treatments can cause tinnitus in humans.

Tinnitus and central pain are often accompanied by altered perception of physical stimuli. Many individuals with tinnitus have signs of cross-modal interactions such as between the auditory and the somatosensory system (Cacace et al., 1994), and tinnitus may be modulated by somatosensory stimulation (Møller et al., 1992; Cacace et al., 1999) (see Chapters 1 and 3). Signs of re-routing of information are common for both tinnitus and central pain. Allodynia⁴ that is often present together with central neuropathic pain is an example of re-routing of information where innocuous somatosensory stimulation become re-routed to pain circuits (Price et al., 2006; Møller, 2006b).

Many individuals with tinnitus have a lowered tolerance for sounds than normal (hyperacusis, see Chapter 15) (Baguley, 2003; Jastreboff and Jastreboff, 2004). Mild painful stimuli may cause an exaggerated reaction and prolonged sensation of pain (hyperpathia) in individuals with neuropathic pain. Hyperpathia thus have similarities to hyperacusis.

Both severe neuropathic pain and tinnitus are often accompanied by affective symptoms (see Chapter 20). Sounds from outside may evoke fear

(phonophobia) in some individuals with severe tinnitus and severe tinnitus may cause depression and suicide. The increased sensitivity to sounds that is often experienced by individuals with severe tinnitus corresponds to hyperalgesia.

Pathophysiology of tinnitus and pain

Subjective tinnitus and central neuropathic pain have many forms and the pathophysiology of these different forms may differ. However, most forms of chronic tinnitus and pain are phantom sensations (Jastreboff, 1990). Phantom sensations are caused by hyperactivity and re-routing of information in the central nervous system (Møller, 2006c). Hyperactivity may be caused by a reduction of inhibitory input from the periphery or increased excitatory input. Input from the ear may be inhibitory in the cochlear nucleus in a similar way as input from A β fibers provide inhibitory input to neurons in the dorsal horn of the spinal cord (and the trigeminal nucleus) that receive input from pain receptors.

The anatomical location of the physiologic anomaly that causes symptoms is often different from that to which the symptoms are referred for both tinnitus and central pain. That the neural activity that causes tinnitus can persist without input from the periphery is evident from the fact that individuals with severed auditory nerve can have tinnitus. This is similar to what occurs in many forms of central neuropathic pain where pain may persist without input from the periphery while being initiated by trauma, inflammation, etc. that affect peripheral nerves.

Central neuropathic pain and many forms of tinnitus are examples of disorders where expression of neural plasticity going awry causes the symptoms (see Chapter 3). The abnormal neural activity that causes tinnitus is often generated in the nervous system without input from the periphery, although it may have been initiated by such abnormal input. The role of expression of neural plasticity in central pain has been studied extensively (Coderre et al., 1993; Doubell et al., 1999; Arendt-Nielsen et al., 2000; Carli, 2000; Price et al., 2006). The fact that some forms of

⁴Allodynia describes a painful sensation from innocuous stimulation of the skin. It occurs often in connection with central neuropathic pain.

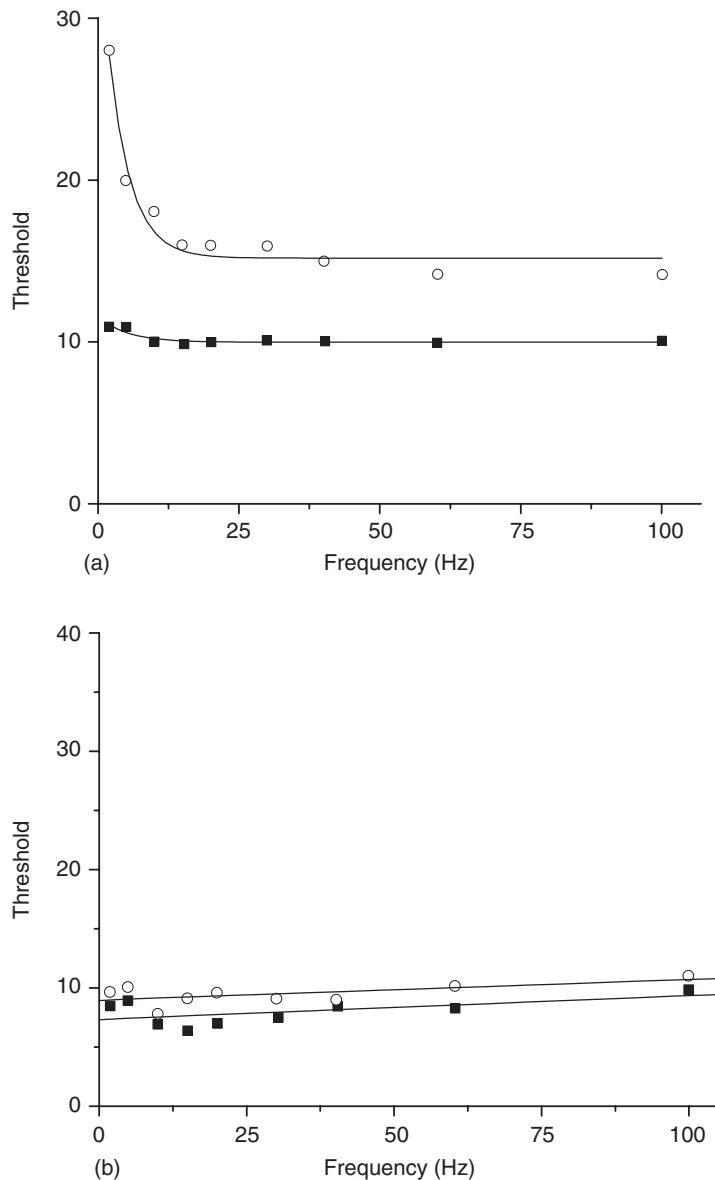


Fig. 1. (a) Threshold of sensation of electrical stimulation of the skin (filled squares) and threshold of pain (open circles) shown as the function of the rate at which the stimulus impulses were presented. (b) Similar graph as in (a) obtained in an individual with chronic pain. Adapted from Møller and Pinkerton (1997) with permission from Maney Publishing.

pain can be reversed by appropriate sensory stimulation (transderm electrical nerve stimulation, TENS) (Willer, 1988), supports the hypothesis that this kind of pain is caused by reversible changes in synaptic efficacy. In a similar way, there is general agreement that many forms of tinnitus are caused

by expression of neural plasticity (Møller, 2003a, 2006a) and tinnitus can often be alleviated by appropriate sound stimulation (in connection with counseling) (Chapters 40 and 41).

The redirection of information that may occur in some forms of tinnitus resulting from

involvement of the non-classical pathways may be similar to that which causes allodynia to occur in connection with central neuropathic pain. The re-routing that causes abnormal cross-modal interactions is assumed to be caused by altered synaptic efficacy or by creation of new synapses or new morphologic connections through sprouting of axons or dendrites through the expression of neural plasticity (Møller et al., 1992; Møller, 2003a). Re-organizations through expression of neural plasticity have been demonstrated in the thalamus (for pain) (Anderson et al., 2006) and the cerebral cortex (tinnitus) (Mühlnickel et al., 1998).

The non-classical (extralemniscal or diffuse) pathways involve the dorsal and medial thalamus whereas the classical (lemniscal or specific) pathways involve the ventral part of the thalamus. The medial and dorsal middle geniculate body (MGB) projects directly to the lateral nucleus of the amygdala (LeDoux, 1992; Møller, 2003b) (Chapter 3) and this may explain the affective components that often accompany severe tinnitus (and chronic pain). The findings that limbic structures are more active in response to sound stimulation in some patients with tinnitus (Lockwood et al., 1998) therefore support the findings that the non-classical auditory system is involved in tinnitus. Activation of this subcortical route may explain why some individuals with tinnitus or pain often have affective symptoms (see Chapter 1).

The pain pathways, known as the anteriorlateral system comprising the spinothalamic, spinoreticular and spinomesencephalic pathways have many similarities with non-classical sensory pathways (Møller, 2003b). One such similarity is that these pathways make use of the dorsal and medial parts of the thalamus.

Peripheral sensitization

Sensitization, peripheral or central, plays an important role in creating tinnitus and pain symptoms. There are several ways in which receptors in the ear and in the body can be sensitized. One way is through the sympathetic nervous system. It is well known that activation of the sympathetic nervous system can sensitize receptors for pain

(Wall and Melzack 1999). Reflex sympathetic dystrophy (RSD) (complex regional pain syndrome; CRPS type I) is a typical example of a severe pain condition in which secretion of noradrenalin from sympathetic fiber located near somatosensory receptors sensitize these receptors. When that occurs to an extent that causes the receptors to be activated without any external stimulation a vicious circle is created because the resulting pain increase the sympathetic activity and hence the secretion of noradrenalin and thus increase of pain. Sympathetic (adrenergic) nerve fibers also terminate near hair cells in the cochlea (Densert, 1975), and it possible that similar sensitization may occur in the ear causing tinnitus when the hair cells become sufficiently sensitized that they activate auditory nerve fibers without any sound stimulation.

Central sensitization

The neural circuits of the somatosensory system in the dorsal horn of the spinal cord (and the trigeminal nucleus) are altered in individuals with central neuropathic pain. The changes that occur in the perception of somatosensory stimuli may be explained by specific changes in the processing that occurs in the dorsal horn especially involving the wide dynamic range (WDR) neurons (Price et al., 1992; Brodal, 1998; Doubell et al., 1999; Møller, 2006b) through central sensitization and through expression of neural plasticity (Coderre et al., 1993). These neurons receive input from several types of mechanoreceptors and from pain receptors in the skin.

There are similarities between the changes that occur in the function of dorsal horn neurons (especially the WDR neurons) in central neuropathic pain and the changes that have been observed to occur in the ascending auditory pathways in animals after treatments that normally cause tinnitus in humans [deprivation of input (Gerken et al., 1984) or overstimulation (Szczepaniak and Møller, 1996)]. There is evidence that neurons in the inferior colliculus and perhaps the cochlear nucleus may undergo similar changes in function as the WDR neurons. Such changes could cause hyperactivity

that could cause tinnitus and re-direction of information to the non-classical auditory pathways.

The processing that normally occurs in the neural circuits in the dorsal horn of the spinal (and the trigeminal nucleus) cord in different forms of pain has been divided in four main states (Doubell et al., 1999). In the normal state, State 1, neural activity elicited by innocuous and noxious stimulations are processed separately and ascend separately to more central regions. The sensitivity of the somatosensory system is reduced in the second stage and that would correspond to hearing loss. The third and fourth states involve sensitization of dorsal horn (or trigeminal nucleus) neurons causing the sensibility to noxious stimulation to increase (hyperalgesia). In this stage cross-modal interaction occurs and normally innocuous stimulation causes pain (allodynia) and pain stimuli cause an exaggerated reaction (hyperpathia). In the third state of processing, it is assumed that the reorganization of the dorsal horn is reversible but in the fourth stage the abnormal state has become persistent. Increased sensitivity to sounds has similarities to the symptoms of pain that are experienced in the third and the fourth states of changes in the processing in the dorsal horn.

Specific changes that occur in the neural processing in the dorsal horn (and the trigeminal nucleus) are often seen after trauma and acute inflammation, and known as neuropathic pain and that resembles the changes that occur in the auditory system immediately after strong sound exposure.

Degeneration of nerve fibers such as from tissue injury (Dubner and Basbaum, 1994) can cause vacant synaptic sites that may be invaded by sprouting of other kinds of fibers (Doubell et al., 1999). This may be similar to what happens in injuries of the auditory nerve such as, most clearly, from the damage done to the nerve from vestibular schwannoma. Although these tumors rarely develop from the auditory nerve, tumor cells invade the nerve. Vestibular schwannoma are always associated with tinnitus. Injury to the auditory nerve may also apply to some forms of nerve injuries such as from surgical trauma or from viral infections.

Different expressions of pain and tinnitus

Tinnitus can cause suffering and it has been hypothesized that such “bothersome” tinnitus is different from tinnitus that does not cause suffering, and that tinnitus that cause suffering activate parts of the nervous system outside the auditory nervous system (Chapter 40). These properties of tinnitus have similarities with pain, which also can cause suffering. Pain can cause the feeling of being either escapable or inescapable, and it has been shown that inescapable and escapable pain use different parts of the periaqueductal gray (PAG) (Keay et al., 2001; Lumb, 2002).

Treatment of pain and tinnitus

While there are general medications (analgesics) that have beneficial effects on many forms of pain, medications with similar effect do not exist for tinnitus. Some forms of severe tinnitus can be successfully treated by exposure to specific sounds together with counseling (Jastreboff and Jastreboff, 2000) (Chapters 40, 41 and 42). Such treatment is based on the hypothesis that proper stimulation can reverse plastic changes in the nervous system. In this way the treatment has similarities with the use of TENS for treatment of central neuropathic pain (Willer, 1988; Price et al., 2006; Møller, 2006b).

The microvascular decompression (MVD) operation is an effective treatment of individuals with some forms of pain (trigeminal neuralgia, TGN) (Barker et al., 1996) and it can eliminate or ameliorate tinnitus in selected individuals (see Chapter 38) (Møller et al., 1993a). Treatment of TGN has a success rate of approximately 85%, similar for men and women (Barker et al., 1996), whereas the success rate for MVD for severe tinnitus is very different for men and women (Møller et al., 1993b) (29% and 55% success, respectively) and overall it is lower than it is for TGN.

Cochlear implants that may provide stimulation of auditory nerve fibers in deaf individuals or individuals with severe hearing loss can also have beneficial effect on tinnitus. Stimulation of the cochlea

by electrodes placed on the cochlear capsule has also shown to be beneficial (Rubinstein et al., 2003).

Stimulation of the cochlea may suppress tinnitus by replacing the lost inhibitory input to the auditory nervous system. This would be similar to stimulation of large somatosensory (A β) fibers that innervate receptors in the skin in individuals with pain using TENS, which would provide inhibitory influence on cells in layer II of the dorsal horn of the spinal cord (or the trigeminal nucleus) that receive input from nociceptors (A δ and C fibers) (Brodal, 2004) (Møller, 2003b). These kinds of treatments may also suppress pain and tinnitus by reversing plastic changes that were caused by deprivation of input.

Magnetic and direct electrical stimulation of the auditory cerebral cortex can suppress tinnitus in selected patients (see Chapters 34, 35 and 36), and electrical stimulation of the somatosensory cortex can suppress some forms of pain (Chapter 36). Such stimulation may reverse re-organization of the cortices, or more likely, may act on thalamic nuclei through the corticothalamic pathways.

It is another similarity between tinnitus and neuropathic pain that both tinnitus and neuropathic pain become more difficult to treat when the symptoms have lasted a long time.

Abbreviations

CRPS	complex regional pain syndrome
MVD	microvascular decompression
PAG	periaqueductal gray
RSD	reflex sympathetic dystrophy
TENS	transderm electric nerve stimulation
TGN	trigeminal neuralgia
WDR	wide dynamic range

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CHAPTER 5

The Darwinian plasticity hypothesis for tinnitus and pain

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Abstract: We present the hypothesis that expression of neural plasticity is a form of adaptation based on natural selection, where cells or cell groups deprived of sensory input actively go and look for information in order to survive. The Darwinian model of brain plasticity can explain the symptomatology induced by deprivation of input which was not well explained by classical plasticity without contradicting pertinent data from the neurophysiological, neuroanatomical, functional neuroimaging, and clinical literature. Applying the concept of Darwinian plasticity to sensory plasticity that causes symptoms and signs of disease might lead to the development of new treatments for deprivation of input induced symptomatology. We will use results from the application of electrical and magnetic stimulation of the auditory and the somatosensory cortices for treatment of tinnitus and for alleviating some forms of pain in support of the Darwinian hypothesis about neural plasticity. We will also review the literature regarding physiological and anatomical, as well as imaging data that support the existence of this hypothetical form of plasticity.

Keywords: Darwin; Darwinian plasticity; deafferentation; neurostimulation; phantom pain; tinnitus; auditory cortex; somatosensory cortex

Introduction

Neuropathic pain and tinnitus are both considered phantom perceptions sharing a similar pathophysiology and clinical symptoms. Both neuropathic pain and tinnitus are perceptions coming from the missing part of the body, and are considered the result of maladaptive plasticity, where cortex not deprived of sensory input expands into the vacated area. Clinically, however, this should result in pain or tinnitus representing lesion-edge characteristics, contradictory to what is noted in real life. We present the hypothesis that expression of neural

plasticity is a form of adaptation based on natural selection, where cells or cell groups deprived of sensory input actively go and look for information in order to survive. Explaining expression of neural plasticity by the concept of Darwinian development solves the clinical conundrum regarding the symptoms and signs of expression of cortical plasticity such as it is believed to occur in some forms of tinnitus and pain. The concept of Darwinian principles of survival of the fittest can explain why input-deprived neurons start processing information from adjacent neurons, namely in order to survive.

This way of viewing neural plasticity provides a theoretical framework for developing new treatments for brain dysfunctions induced by

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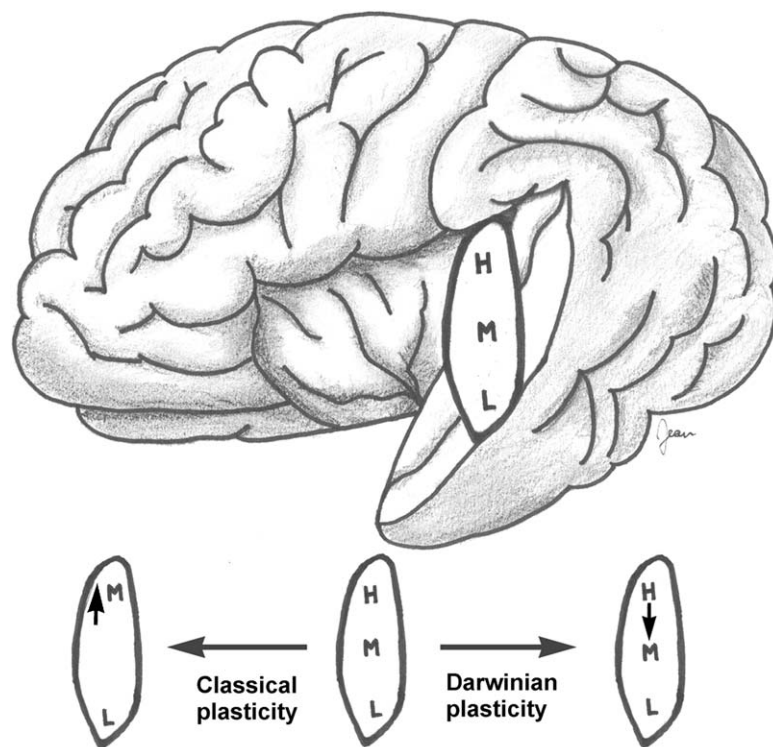


Fig. 1. In classical plasticity the non-deprived lesion edge frequencies expand into the deprived area, in Darwinian plasticity the deprived frequencies will look for information in the adjacent area. Example of the differences in high frequency hearing loss (drawing by Jan Ost).

deprivation of input. Based on this hypothesis, treatments can be developed for disorders that are caused by deprivation of sensory input. The basic concept being that supplying the missing information directly to the deafferented area will suppress deafferentation-induced symptoms, by preventing or reversing Darwinian plasticity.

To test this hypothesis we have analyzed the results from treatment of patients with phantom sound (= tinnitus) and patients with phantom pain by electrical stimulation of the auditory cortex and the somatosensory cortex respectively (Chapter 36).

In the following we review neurophysiological, neuroanatomical, and functional imaging data, and suggest that the generally accepted hypothesis that topographic map plasticity changes seen in reorganization are not only due to ingrowths of synapses into an area of deprived input, but that the opposite might also be occurring: input-deprived synapses could sprout to adjacent non-deprived

areas in an attempt to survive in long-term reorganization. Similarly, short-term reorganization could involve input-deprived neurons processing information from adjacent neurons by changing synaptic efficacy. Figure 1 shows how sprouting in the auditory cortex would occur within an area where neurons are tuned to similar frequencies. Darwinian hypothesis of plasticity suggest that sprouting occurs between areas where neurons are tuned to different frequencies, for example, from high frequency areas to areas where neurons are tuned to middle frequencies.

Darwinian hypothesis of neural plasticity

The human brain can be considered the result of a Darwinian evolutionary development (Calvin, 1987). A synapse can be seen as the analogue of a biological creature, replication and growth of

connections the analogue of organism reproduction, and in this view, competition for connections is the analogue of competition for food and mates, and which connections survive is based on its environment and the competition (Deacon, 1997). Neural connections that are fit for the environment survive and can be strengthened or weakened, much the same as individuals that fit the environment. Neurons that are fit follow the same rules (proliferation and apoptosis), analogous to whole species. This evolution-like process for building brains allows brains to become adapted to the bodies they inhabit within their own internal constraints, with a minimum of pre-planned design: brains are not genetically hardwired, but only the rules coding for self-organization via Darwinian competition are coded for (Deacon, 1997). This axonal competition for target territories furthermore results in development of topographic maps such as the visuotopic map, somatotopic map of the motor and sensory cortex and the tonotopic map of the auditory system.

Plasticity refers to the capacity of the nervous system to modify its organization (see Chapter 2) (Bavelier and Neville, 2002). This is more pronounced in the developing brain but the mature auditory system still has the capacity for reorganization, adjusting itself to changes in the auditory environment.

One form of neural plasticity regards the tonotopic maps of the auditory cortex. These maps are not rigid and may reorganize under influence of physiological (Gao and Suga, 1998) or pathological (Suga et al., 2000) sensory stimuli. Similar modification of tonotopic mapping in the entire auditory pathways may be artificially induced by focal electrical auditory cortex stimulation (Suga et al., 2000; Zhang and Suga, 2000; Suga and Ma, 2003). This adaptive plasticity can be both beneficial, such as in learning and repair or maladaptive, resulting for example in tinnitus. The same holds for the mature somatosensory system: any alteration of somatosensory input, whether physiological (Recanzone et al., 1992) or pathological (Kaas et al., 1983) can induce a topographical reorganization in the somatosensory cortex.

Topographic reorganization has been demonstrated in humans by means of magnetic source

imaging (MSI) (Flor et al., 1995; Muhl nickel et al., 1998) and functional magnetic resonance imaging (fMRI) (Melcher et al., 2000; Maihofner et al., 2003). Furthermore there is a clear correlation between the amount of reorganization and the intensity of the phantom percept, associated with this sensory cortex reorganization, whether tinnitus or phantom pain (Flor et al., 1995; Muhl nickel et al., 1998). Successful treatment of the phantom perception reverses the reorganization electrophysiologically (Theuvenet et al., 1999; Maihofner et al., 2004).

Cortical areas that have been reorganized, as visualized by fMRI are the targets for supplying the missing information, in attempts to normalize function. We have used non-invasive fMRI guided neuronavigated transcranial magnetic stimulation (TMS) (De Ridder et al., 2004, 2005b) for that purpose. If successful, the clinical suppression of the phantom perception can be perpetuated by implantation of an electrode in the same fMRI based neuronavigated way (see Chapter 36) (De Ridder et al., 2004, 2005a).

Basis for the Darwinian hypothesis

Neurophysiology

Kaas and Schwaber have used closely spaced microelectrode recordings to determine the receptive fields of cortical neurons in monkeys creating a detailed tonotopic map of the A1 cortical area. After inducing a high-frequency lesion by administering ototoxic antibiotics (kanamycin) combined with furosemide (Schwaber et al., 1993) that preferentially lesion high-frequency hair cells, they studied the concomitant changes in the tonotopic maps of the auditory cortex. Recording from neurons that normally responded to high-frequency tones, they found these neurons now responded to tones of lower frequencies (mid-frequency). These findings were interpreted to show that synaptic connections had been established with neurons that previously responded to high frequencies. Similar studies in deafferentation pain by the same group yielded findings that were interpreted in a similar way (Kaas et al., 1983).

However, these results might also be interpreted from a Darwinian point of view to indicate that high-frequency neurons deprived of sensory input begin to process information from adjacent non-deprived areas by changes in synaptic strength (in short-term reorganization), or by sprouting of dendrites into the adjacent area that were not affected by the deprivation of input (in long-term reorganization). Such cells will respond to mid-frequency tones as well. Thus electrophysiological data support both explanations of the alterations that are caused by deprivation of input. Thus anatomical and other data are necessary to distinguish between the two possible forms of plasticity.

Neuroanatomy

While plenty neurophysiological data exist characterizing topographic (re)organization of central maps, the underlying anatomical correlates have not been thoroughly investigated. That dendrites of neurons that are deprived of input can anatomically sprout into the adjacent areas in the auditory system has at least been demonstrated in the cricket (Hoy et al., 1985; Brodfuehrer and Hoy, 1988). For the somatosensory system, dendritic arbors are noted to expand distally reaching into non-deprived cortical areas (Churchill et al., 2004), suggesting that sprouting occurs from deprived toward non-deprived areas and not in the opposite direction. These anatomical observations favor the Darwinian hypothesis of neural plasticity.

Clinical experience

Both in the auditory system (Norena et al., 2002) and in the somatosensory system (Ramachandran and Hirstein, 1998), auditory phantom perceptions (tinnitus) and phantom pain are those coming from the missing part of the body. The tinnitus spectrum a patient perceives is found to occupy a wide frequency range corresponding largely to that at which hearing thresholds are abnormally elevated (Norena et al., 2002), and phantom pain is perceived in the missing body part. Darwinian plasticity also more accurately explains how tactile stimuli of the face demonstrate a hand representation in

individuals with an amputated arm (Ramachandran and Hirstein, 1998) than conventional hypotheses about neural plasticity. If cells that represent the hand in the somatosensory cortex have sprouted into the non-affected adjacent face area these cells that were deprived of their normal input will be activated by touching the face (Ramachandran and Hirstein, 1998; Ramachandran and Rogers-Ramachandran, 2000). If on the other hand the dendrites of the neurons that receive normal input would have sprouted into the vacated arm area on the sensory cortex, hand perception as such would have disappeared altogether. Our clinical case with the abnormal perception of the location of the eye (Chapter 36) can be explained in a similar way, where the sensory-deprived supraorbital area is the one that is painful. The phantom eye perception may be explained in a similar way. If the neurons that receive normal input would have sprouted towards the neurons that receive input from the V1 (forehead) area that is deprived of input, it would have caused the phantom eye to be localized on the forehead. It was this clinical picture that inspired us to question the accepted pathophysiological hypothesis of reorganization through expression of neural plasticity in response to deprivation of input.

Functional imaging

A further argument favoring the Darwinian hypothesis for plasticity comes from magnetoencephalographic (MEG) studies. Thus Muhlneckel (Muhlneckel et al., 1998) and Flor (Flor et al., 1995) using MSI explored the reorganization of the auditory cortex that occurred in patients with tinnitus. They found a shift of the cortical representation of the tinnitus frequency into an area adjacent to the tonotopic location of the frequency of the tinnitus. They also found a strong positive correlation between the subjective strength of the tinnitus and the degree of cortical reorganization, similarly to what has been shown for the somatosensory system (Flor et al., 1995). The amount of phantom limb pain is highly correlated with degree of cortical reorganization of the primary somatosensory cortex (Flor et al., 1995).

If the reorganization consisted of invasion from the non-deprived adjacent area into the deprived area, as has been generally accepted, there would be a shift in the magnetic source of the adjacent frequencies, and not the deprived frequencies as noted in both of the MEG studies mentioned above (Flor et al., 1995; Muhn timer et al., 1998).

It has been demonstrated that the BOLD effect on fMRI correlates with event-related synchronization in the gamma band (32–38 Hz), both in EEG (Foucher et al., 2003) and MEG (Brookes et al., 2005) studies. This suggests that fMRI (Smits et al., 2004) can visualize the gamma band synchronized activity associated with tinnitus and pain (Llinas et al., 2005).

Brain stimulation

A last argument favoring the Darwinian hypothesis for neural plasticity comes from studies of electrical stimulation of sensory cortices (De Ridder et al., 2006, , 2007a, b). Low-frequency stimulation (<120 Hz) activate cells as demonstrated in the human subthalamic nucleus (Beurrier et al., 2001), whereas high-frequency stimulation inactivate cells in a ‘functional lesion’ (Benabid et al., 2005). Both tinnitus (Eggermont and Roberts, 2004) and neuropathic pain (Chudler et al., 1990) are associated with hyperactivity of their respective primary sensory cortices. Our stimulation parameters, consisting of (activating) low-frequency stimulation should worsen tinnitus and pain if the adjacent areas have sprouted into the deprived areas, as they would then be stimulated even more, based on the egocentric selection principle (Suga et al., 2000). On the contrary, in a Darwinian model of brain functioning, supplying low intensity electrical stimuli to synapses of cells that are deprived of input would prevent (or reverse) such cells to sprout (prevent the looking for information in order to survive), thereby clinically preventing (or reversing) the phantom perceptions. Electrical stimulation of sensory cortices may supply the missing input directly and high-intensity stimulation would be predicted to induce tinnitus and pain, as seen in our patients (De Ridder et al., 2006, 2007a, b).

Conclusion

Neurophysiological and neuroanatomical data, functional imaging, and clinical experience support the Darwinian hypothesis for explaining symptomatology caused by deprivation of input, better than a classical reorganization model. Darwinian plasticity models can help in devising effective treatments for brain dysfunction caused by deprivation of input, such as some forms of tinnitus and neuropathic pain.

Acknowledgments and financial disclosure

No external funding was used for this study. The authors thank Jan Ost for the artwork.

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CHAPTER 6

The relevance of spontaneous activity for the coding of the tinnitus sensation

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Abstract: In this chapter we will present support for the hypothesis that *synchronous* neuronal activity of cell assemblies within the auditory cortex could be the underlying neural code of tinnitus. Such synchronous activity is reflected in the ongoing oscillatory activation pattern that can be recorded non-invasively using MEG and EEG techniques. We conclude that such an *oscillatory model of tinnitus* can explain many different observations regarding tinnitus.

Keywords: tinnitus; spontaneous activity; oscillations; magnetencephalography

Introduction

Subjective tinnitus is the sensation of a sound when an identifiable physical source of this perception is absent (see Chapter 1). There is considerable evidence that a lesion in the peripheral auditory system can result in reorganization of central nervous system structures (auditory, but also limbic areas), which may lead to neuronal signals that cause phantom sensations (see Chapters 2 and 3). The most common cause of tinnitus is damage to the receptors of the inner ear. The fact that transection of the auditory nerve does not abolish the tinnitus sensation is strong evidence for the central hypothesis for tinnitus. Animal studies have provided evidence that tinnitus is not associated with hyperactivity of the auditory nerve (Muller et al., 2003), but many studies have found evidence that abnormal (increased) synchrony is involved in tinnitus (see Chapters 2 and 6).

This chapter outlines a model of how *integrated* neuronal activity in the auditory cortex changes following a peripheral lesion that causes tinnitus. In humans with tinnitus this can be best studied using non-invasive electroencephalography (EEG) and magnetencephalography (MEG). The model can be tested and elaborated upon and serve as a base for the treatment of chronic tinnitus. One such clinical approach that has been suggested by the outcome of our recent experimental studies shows that oscillatory brain activity is modified in tinnitus, both in frequency and space (see Chapter 46 for further details).

Deafferentation is essential

Tinnitus is usually triggered by a dysfunction or lesion in the ear or the auditory nerve. Based on a survey of 5000 tinnitus sufferers, Goebel et al. (2005) found that 80% report some form of hearing impairment. With these investigators' definition of hearing loss however, apparently a

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considerable proportion of individuals with tinnitus (20%) do not have hearing loss and thus have presumably normally functioning hearing. At first glance this supports the view that tinnitus is not necessarily linked to hearing loss and that there may be at least two essentially different forms of tinnitus (e.g., one triggered by peripheral damage and one without any hearing loss). Yet this hypothesis is problematic for two reasons: (1) a transient hearing loss may trigger a reorganization within the auditory system that is maintained even when the hearing function becomes restored. (2) The usual criterion for hearing loss is the clinical audiogram. However, this is a rather incomplete and thus poor assessment of hearing for the following reasons: (1) in almost all individuals with tinnitus whose hearing thresholds according to their audiograms were regarded to be within normal limit had abnormal distortion product of otoacoustic emissions (Shiomi et al., 1997) indicating outer hair cell dysfunction. (2) Sharp increased thresholds assessed via the threshold equalizing noise (TEN) test were found in young individuals with tinnitus who had normal (clinical) audiograms, a finding which implies deafferentation (probably inner hair cell damage) in a circumscribed frequency range (Weisz et al., 2006). The TEN test was proposed by Moore et al. (2000) as a screening tool for identifying dead regions on the cochlea. Different from the standard audiogram, the presentation of the pure tone for which the threshold should be assessed is accompanied by a noise that contains equal energy across different auditory filters. When subjects identify the pure tone with functional inner hair cells then thresholds should be close to noise intensity. If the threshold is strongly above (~ 10 dB) the noise intensity, then this indicates that the sound is detected by neighboring hair cells. Essentially the TEN is a method to complicate this kind of “off-frequency” listening. (3) Sharp transitions between normal and abnormal hearing — described by the gradient (dB/octave) of two neighboring frequencies as it appears in the clinical audiogram — was found to be indicative for the presence of tinnitus by König et al. (2006).

All these results point to the involvement of hearing loss or sharp discontinuities in the

audiograms in the generation of tinnitus. Deprivation of input likely results in a reduced capacity of affected neurons to inhibit excitatory input from undaunted neurons located close to the lesion-edge. This in turn is expressed in various changes of central nervous activity of which one (or more) variant could be the neuronal “signature” of tinnitus (Eggermont and Roberts, 2004).

Beyond map reorganization

One of the effects of a diminished inhibitory capacity is an enlarged representation of sounds in the undamaged regions of the edge of the frequency region that is deprived of input. This means that deprived neurons become responsive to frequencies adjacent to the cortical regions that represent the frequency range where hearing is damaged (so called lesion-edge frequencies). In the somatosensory modality it has been shown that this type of map reorganization is a very fast process, appearing immediately after an amputation of a limb (Calford and Tweedale, 1988). Since morphological reorganization — such as a morphological change of synaptic connectivity with an alteration of synaptic strengths — requires time (at least minutes; Lüscher et al., 2000), the immediateness of the effects has to rely on pre-established connections that are normally silent. On the other hand fast changes (i.e., those realized through migration of receptor proteins into the membrane) usually precede morphological alteration of the synapse (Lüscher et al., 2000). Studies in the chick have shown fast changes in protein synthesis from deprivation of input (Sie and Rubel, 1992). Consequently, if hearing results from loss of hair cells, i.e., a kind of “cochlear amputation” then tinnitus could be the auditory analogue of the somatic phantom pain.

It has been shown in the somatosensory system that the reorganization of the somatotopic map after limb amputation is highly correlated with the amount of reported phantom limb pain (Flor et al., 1995). This would suggest that tinnitus could be related to tonotopic map changes (Mühlnickel et al., 1998). Animal experiments confirm an overrepresentation of lesion-edge frequencies following

an experimental treatment that would induce tinnitus in humans (Irvine et al., 2001). Moreover, distortions of the tonotopic gradient in subjects with tinnitus have been demonstrated in humans by means of MEG and magnetic source imaging (Weisz et al., 2005b; Wienbruch et al., 2006). It seems important to note that all these observed changes in function were correlational and not causal in nature. An injury, for instance, may trigger another type of plastic alteration in the central auditory system (or beyond) besides map reorganization, and that change may be that what causes tinnitus (see Chapter 3).

Given the network character, it is, however, conceivable that the two processes are somehow linked. Norena and Eggermont (2005) demonstrated in cats that massive high frequency auditory input (enriched acoustic environment) following noise trauma reduced the extent of hearing loss as well as signs of tonotopic map reorganization in the primary auditory cortex. It will be of interest to see if such stimulation affects tinnitus in humans.

In addition, there is a central reorganization in neural networks that is probably not directly linked to map reorganization and that is expressed in characteristic alterations of ongoing spontaneous activity extending much beyond the location of the altered tonotopic map (Weisz et al., 2005a). It remains to be tested how closely the two phenomena are linked to each other. In the following, we will present the hypothesis that tinnitus is more directly related to the changes in the responses pattern of neurons, especially their oscillatory behavior than to map reorganization, and that retuning of the former modifies tinnitus (see Dohrmann et al., this volume). Additionally, the same enriched acoustic environment mentioned previously also prevents changes of spontaneous activity putatively linked to tinnitus (Norena and Eggermont, 2006).

Tinnitus and variants of spontaneous activity

As the title of this chapter suggests, spontaneous activity is a rather *generic* term used here to address any neuronal activity that is *not evoked or*

driven by an external event. This is an important point as this definition overlaps with that of the definition of tinnitus. The term spontaneous activity can be a constant source of confusion, as it may describe features on various scales — from firing of single units to oscillatory activity of large cell assemblies — which strongly depends on the background of the researcher and the individual with tinnitus (human, animal) who is investigated. We will first give a short description of findings from animal research, which usually focuses on spontaneous activity of a single neuron or a few neurons. Subsequently, a brief introduction to oscillatory brain responses will be given. Oscillatory responses can be studied in humans using non-invasive techniques. We will show that this is also the level of neuronal activity that is likely to be related to higher order cognitive functions, such as perception and attention.

Insights from animal studies

As mentioned above one of the basic assumptions regarding tinnitus is its relationship to a reduced inhibitory capacity of neurons that are deprived of input. This is supposed to lead to a hyperactivation of neighboring neurons that are not deprived of input characterized by increased neuronal firing rate. The only level of the auditory nervous system where this has been consistently shown appears to be the dorsal cochlear nucleus (Kaltenbach, 2006). For the inferior colliculus, reported results are inconsistent. While Chen and Jastreboff (1995) find increases in firing rate following administration of salicylate to induce tinnitus, significant decreases relative to baseline were reported by Ma et al. (2006) using doses of salicylate proven to be sufficient to induce tinnitus. Yet spontaneous firing rates increased after exposure to noise that was assumed to have induced tinnitus as reported by Ma et al. Since both exposure to noise and the administration of salicylate were expected to have caused tinnitus enhanced firing of neurons in the inferior colliculus does not appear to be a consistent neuronal correlate of phantom sound perception. Results from similar studies of the auditory cortex are not conclusive either, with

varying results depending on the way tinnitus is induced. Increased firing was noticed by Norena and Eggermont (2003) in the primary auditory cortex following noise trauma, but a reduction is seen when tinnitus is elicited by salicylate (Eggermont and Kenmochi, 1998). Increases in firing rate of neurons in the secondary auditory cortex following salicylate and quinine application have been reported (Eggermont and Kenmochi, 1998).

Interpretation of results from animal experiments are hampered by the anesthesia used which may affect the results in unknown ways. Yang et al. (2006) pointed out that after administration of anesthesia the mean spontaneous firing rate (even in studies reporting hyperactivity) was still on the order of 7–11 times lower than in non-anesthetized animals. For awake rats these authors found that administration of salicylate reduced spontaneous firing rate (hypoactivity). These results that should exemplify that a pure hyperactivity logic appears to be insufficient is furthermore corroborated by the temporal evolution of these spontaneous rate effects (Eggermont and Roberts, 2004): after intense noise exposure enhancements of firing rate in the primary auditory cortex develop after a few hours (Norena and Eggermont, 2003) and even 2–5 days in the dorsal cochlear nucleus (Kaltenbach et al., 2000). This contrasts with the normally rapid onset of tinnitus following noise trauma.

Given these findings, it is likely that the mechanisms causing the tinnitus are likely to go beyond a pure quantitative excess of activity in the form of an increased neuronal firing rate. An alternative would be that distinct *populations* of neurons within the auditory cortex coding the phantom percept *synchronize* their firing. Such synchronization may accompany an overall increase in firing, but not necessarily be tied to that (see also Chapter 2). Summation of post-synaptic potentials induced by synchronized input is stronger than that from asynchronous spikes, thus prioritizing features that are coded via synchrony for further processing (Niebur et al., 2002). Spike synchronization has been particularly well-studied in the visual modality, where it has been associated with representation of stimulus features within a cell

assembly and binding of features across distributed assemblies into conscious percepts (see Singer, 1999 for an extensive review).

Far less is known about the role of such synchronization in the auditory system; yet it is imaginable that the tinnitus percept could arise through “intrinsically” generated synchrony, i.e., unrelated to an external presentation of an auditory stimulus. The ensemble firing created would then attain more saliency than dispersed firing and be interpreted as real sound at subsequent processing stages. Prolonged synchronous firing then will lead to use-dependent synaptic modifications (long-term potentiation, LTP), creating a *stabilized* tinnitus related cell assembly with time. Indeed there is some evidence that this might occur: Synchronous spiking (normalized for the total number of spikes) has been shown to increase in the primary auditory cortex of cats following noise trauma (Norena and Eggermont, 2003; Seki and Eggermont, 2003). Importantly, the change to synchronized firing appears to occur more rapidly than changes in firing rate, (Norena and Eggermont, 2003; Seki and Eggermont, 2003) after noise trauma. These findings have been obtained in animals being under anesthesia; albeit under a state where it seems even more challenging than normal to know whether they may be accompanied by correlates on a perceptual level. There is therefore a need to study synchrony in unanaesthetized animals and such studies should be complemented by electrophysiological studies in humans.

Work in humans: oscillations reflect integrated activity from neuronal assemblies

Intracranial recordings of spike activity of single or multiple units in humans is possible only under exceptional circumstances, often limited to pathological conditions of one kind or another. To the best of our knowledge there have been no reports to date regarding local field potentials (LFPs) from the auditory cortex in humans with tinnitus. Non-invasively, spontaneous activity can be recorded by means of EEG or MEG. It is important to stress once again that this is *not* identical to what is commonly meant by spontaneous activity in

animal studies, which refers to firing properties in general and not necessarily to synchrony. EEG and MEG on the other hand represent the ensemble electrical activity (i.e., from their post-synaptic potentials) of large *neuronal populations or cell assemblies*. Apart from being non-invasive, these methods have the distinct advantage of giving access to assembly activity as it unfolds in *real time* (only limited by the sampling rate). A disadvantage is that simultaneous activities overlap and, consequently, the anatomical location of the activity that is recorded from the scalp cannot be inferred directly from the data (or sometimes not at all). The anatomical location of the sources can only be approximated via inverse solution strategies that rely on certain assumptions.

Oscillatory activity has been and still is frequently associated with different cognitive or pathological states. Since the EEG/MEG signals represent the combination of excitatory and inhibitory post-synaptic potentials, *oscillatory activity can be regarded as an integration of input*. Analysis, such as frequency (spectrum) analysis or autocorrelation analysis, can provide quantitative information about oscillatory components of recorded electrical potentials such as EEG. Wavelet analysis can provide time-frequency representation relative to an external or internal event. Furthermore, changes in the post-synaptic potentials alter the probability of spikes (i.e., output), so *oscillatory activity also reflects fluctuations in neuronal excitability*. It has been shown, for example, that spike synchronization is accompanied by rhythmic firing in the gamma range, itself closely related to the oscillatory response of the LFP (Gray and Singer, 1989). Also, spike-triggered averaging has revealed concomitant gamma activity in the LFP (Fries et al., 2001). Yet, spiking and gamma activity appears also to be modulated by slower frequency oscillations (Lakatos et al., 2005; Lee et al., 2005). It is one of the fascinating aspects of brain function that oscillatory activity is self-organizing, i.e., under certain circumstances activation properties of single cells turn into population properties via synchronization. The integrated activity leads to behaviors, sensations, feelings, etc., putting oscillatory brain activity at the interface of the mind–body problem.

Tinnitus and ongoing oscillatory activity in humans

A large amount of data has been acquired from studies of animal models of tinnitus. Only very little is known about the relationship of ongoing spontaneous activity and tinnitus in humans despite the known behavioral importance of large-scale oscillatory activity. The great majority of electrophysiological studies in humans with tinnitus are still guided by an event-related approach, i.e., by averaging signals obtained after presenting an event. In a series of studies, our group has focused on spontaneous neuronal activity. We have specifically studied the involvement of different frequency bands in the generation and maintenance of tinnitus and the results serve as elements of a neural oscillation model of tinnitus. The results will be summarized below. We will not cover event related/driven oscillatory activity such as steady-state responses, which is also an active area of research in our group (Schlee et al., 2007; Wienbruch et al., 2006).

In one approach (Weisz et al., 2005a), we assessed 5 min of resting MEG activity in patients with tinnitus and compared the power spectra to those of normal hearing controls. The main differences were markedly reduced alpha power (8–12 Hz) and an increased low-frequency power (delta; 1–4 Hz). These differences were most pronounced bilaterally over perisylvian areas, thus potentially stemming from auditory cortex. The abnormalities in the activity recorded over fronto-temporal regions were significantly correlated to tinnitus-related distress. This finding leads to the hypothesis that tinnitus encompasses a distributed network of neurons in different brain regions including auditory and non-auditory areas that process basic (phantom) sound sensation and related affective and motivational aspects respectively (see also Schlee et al., 2007).

Other parts of our recent research concern how the observed abnormal spontaneous activity pattern is related to perception of sound. As mentioned above there are reasons to believe that synchronous neuronal activity in the gamma band could underlie conscious perception of sound, which includes tinnitus. In a recent study (Weisz et al., 2007), we focused on the high frequency

oscillatory dynamics in patients with tinnitus and normal-hearing controls particularly during periods of enhanced slow-wave activity: pronounced peaks in the 2–7 Hz band-pass filtered and Hilbert-transformed data were used to identify these periods. This work yielded three important findings: (1) the time-course of the slow-wave activity was strongly correlated to activity in a frequency band between 50 and 60 Hz, particularly in controls. (2) Overall, activity in the gamma band was increased in individuals with tinnitus. (3) Activity \sim 55 Hz was significantly associated to the laterality of the tinnitus percept. This is the frequency range (50–60 Hz) that was modulated by slow-wave activity in controls, implicating in general a coupling between these bands. Individuals with unilateral or unilaterally dominant tinnitus had stronger 55 Hz activity contralateral to the reported sensation, whereas subjects with equally strong tinnitus on both sides showed no such lateralization. We interpreted these finding to indicate that the enhanced gamma activity reflect the synchronous firing of neurons within the auditory cortex. This means that the observed gamma activity could be the neurophysiological correlate of basic sound perception. We will elaborate on that below and integrate the interpretations of the different findings.

A single measurement of resting spontaneous EEG/MEG activity does not answer the question about how abnormalities in ongoing oscillatory activity may be related to tinnitus. Attempts to modify ongoing spontaneous activity and measure changes in the perception or, manipulate the tinnitus and observe concomitant changes in brain activity are methods that are likely to contribute to understanding of how the electrophysiological abnormalities in tinnitus patients are related to the tinnitus and its character. The first strategy is currently being tested using neuro-feedback in which the aim is to normalize the spontaneous activity pattern by enhancing alpha power and reducing delta power. Preliminary results indicate that concomitant changes in *both* bands lead to the greatest reductions of tinnitus loudness (for detailed information see Chapter 46). The other strategy consists of reducing the intensity of the tinnitus and to observe whether concomitant changes occur in the

electrophysiological activity. One way to achieve changes in loudness is by using the phenomenon of residual-inhibition (RI) (see Chapter 47), which is a transient reduction in the tinnitus intensity (or even an abolished sensation) that outlasts the duration of a masking sound. We have tested the effect of an RI sound as compared to a control sound on spontaneous activity in eight individuals with tinnitus (Weisz et al., 2007). The most pronounced effect was a significantly reduced delta activity for the RI sound only (see Fig. 1). Overall, the behavioral effects, however, were rather weak but we would expect larger effects in connections with greater reduction of tinnitus through RI. Nevertheless, this study, as well as the others presented here, indicates that some forms of tinnitus may be caused by abnormal spontaneous activity pattern in ensembles of neurons, and that it could be possible to achieve significant relief by normalizing this pattern of neural activity.

Concluding remarks and a model proposal

In this chapter we have elaborated on the hypothesis that tinnitus may be the consequence of an enhanced level of synchronous firing of neurons in the auditory cortex in absence of any external activation. On a more macroscopic level these changes are associated with an altered pattern of ongoing oscillatory activity as can be measured non-invasively in humans using EEG and MEG. We are not aware of any studies reporting spontaneous LFP activity in awake animals following tinnitus induction. It would be of great interest and importance to relate spontaneous activity LFP data in animals to human EEG/MEG data and vice versa.¹ Certainly focusing only on a cortical level constitutes an oversimplification as abnormalities can be also observed at subcortical levels

¹Even though neuroimaging data (PET, fMRI) can contribute some interesting aspects in interpreting electrophysiological data it is necessary not to confuse the methods. Neuroimaging methods essentially measure changes in metabolism and cerebral blood flow and the relationship with neuronal activity is by no means clear. There is some evidence that the BOLD response reflects local field potentials and particularly gamma activity (Logothetis, 2002), yet more recent studies cast doubts that there is a direct relationship (Burke and Buhrle, 2006).

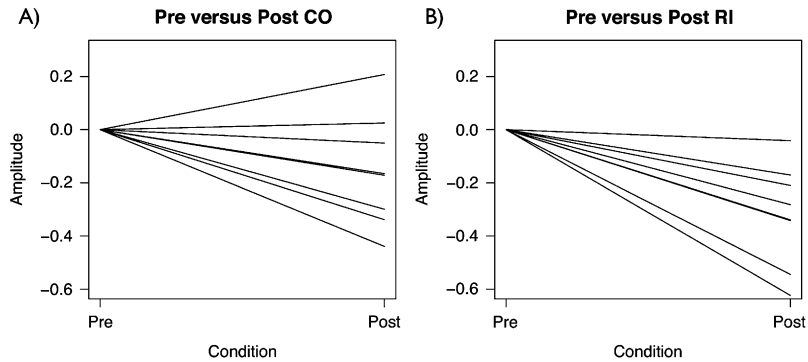


Fig. 1. Delta activity for a period pre and post presentation of two masking stimuli. One stimulus (RI) induced a more pronounced residual inhibition than the other (control, CO). Each subject is depicted as a line and the pre value was set to zero in order to better visualize the changes. The RI sound reduced slow-wave activity in every single subject, whereas a greater variability was present for the CO stimulus.

in animal models of tinnitus. While it may seem logical to assume that the lowest level in the auditory system showing abnormal neuronal activity must be the place of origin of the tinnitus sensation, this hypothesis is flawed for several reasons. The auditory system comprises feed-forward *and* feedback circuits that cause complex interactions between different parts of the system. The fact that the fibers from the auditory cortex to the medial geniculate body outnumber the thalamocortical ones by a factor ten (Eggermont, 2003) is a strong sign of such interaction and indicates that spontaneous activity (as well as tonotopic maps) can be altered in a descending manner as well (Suga and Ma, 2003).

This leads to our first conclusion that an altered pattern of ongoing oscillatory activity in the auditory cortex is the underlying neural code of tinnitus. In particular, enhancements in the gamma frequency band, which can be assumed to be a sign of enhanced synchronized firing of neurons, appear to be involved in the formation of a conscious percept of phantom perceptions such as tinnitus. How are changes in neural activity reflected in other frequency bands of the EEG? Slow-wave activity may reflect so-called low-threshold spike (LTS) bursts generated in thalamic nuclei as a consequence of hyperpolarization (Llinas et al., 1999; Jeanmonod et al., 1996). However, the relation of such activity to tinnitus is unknown. On the other hand, it is well known that the cortical

architecture is rich in inhibitory interneurons (InhIn) that enable rapid modification of cortical neuronal activity. Bursting activity is also not normally evident in the auditory cortex (Eggermont and Roberts, 2004) or only transiently following noise trauma (Norena and Eggermont, 2003). Furthermore, slower synaptic changes (perhaps implied in stabilizing the “tinnitus cell-assembly”) mainly affect intracortical excitatory synapses (layer 2/3), rather than thalamocortical synapses (layer 4; Foeller and Feldman, 2004). For these reasons, our oscillatory model assumes that the relevant processes leading to the phantom sound take place on a cortical level. This model is an extension of the model proposed by Eggermont (Eggermont and Roberts, 2004) in which we have incorporated oscillatory brain activity.

First, we assume that damage to the cochlea essentially leads to a deprivation of neurons tuned to frequencies that correspond to the frequencies where the hearing threshold is elevated, while sparing neurons that are tuned to other frequencies (indicated by the arrow thickness in Fig. 2). Neurons in the nuclei of the ascending auditory pathways including the cerebral cortex are arranged tonotopically and ultimately form the cortical representational map. In a simplified description, the auditory cortex may be regarded as consisting of a layer of excitatory pyramidal neurons (ExPy) and InhIn. These neurons interact via inhibitory or excitatory intracortical synapses

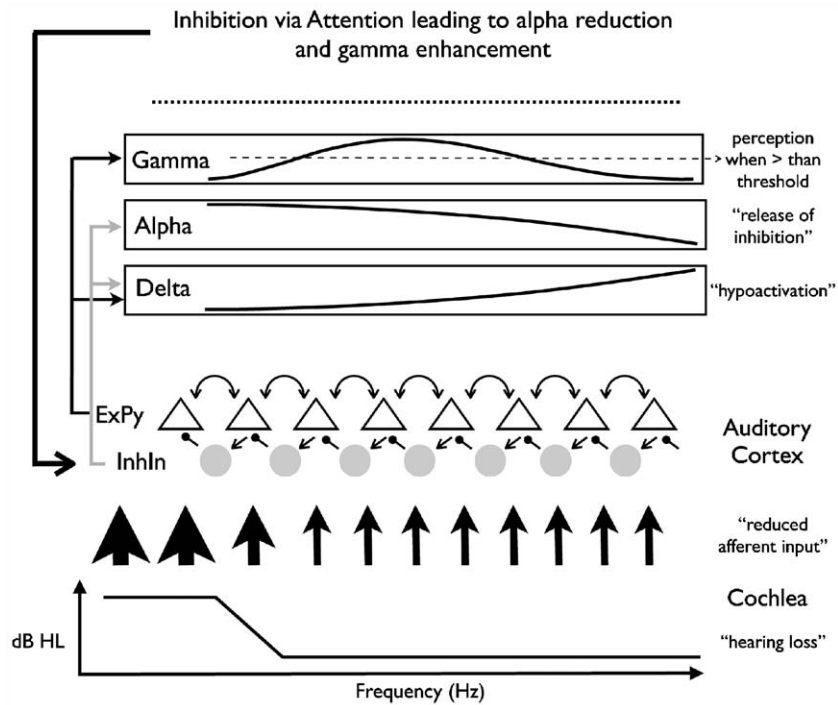


Fig. 2. Oscillatory model of tinnitus. Input deprivation is indicated by an increased threshold in dB HL and reduced line thickness. This leads to reduced activity ("hypoactivation"), marked by an increasing delta activity along the tonotopic axis. A reduced activation of inhibitory neuronal units changes the normal synchronization frequency, which is hypothesized to be in the alpha range (see decreasing alpha slope along tonotopic axis). At a spatial location, where firing probability of excitatory pyramidal neurons is increased via a "release of inhibition" and at the same time affected minimally by hypoactivation (i.e., in principle still responsive), a circumscribed region of gamma activity should emerge. This high-frequency synchronization of neuronal activity putatively underlies the sound perception. The activational pattern can furthermore be modulated attention, which is hypothesized to act mainly on the inhibitory neurons. See text for a detailed explanation. ExPy, excitatory pyramidal neurons; InhIn, inhibitory interneurons.

(for simplicity the inhibitory connections to excitatory neurons with higher characteristic frequencies (CFs) are omitted as are the excitatory connections between neurons with lower CF and the inhibitory neuron).

A critical assumption of this model is that under a condition of no external input the normal synchronizing activity of InhIn will be in the alpha range. This is in accordance with the framework of Miller, (2006) who assumed that: (1) EEG alpha activity reflects a hyperpolarized ("down") state of a neuronal assembly, the positive peaks of which coincide with the bursting activity that can be recorded intracranially. (2) Bursting activity (interspike intervals < 10 ms) itself makes activation of InhIn via pyramidal cells more likely, keeping the neuronal assembly in a "down" state. However,

a deafferentation would modify the balance of interactions, possibly resulting in a massive change of the set of attractors in this non-linear system. Reduced afferent input reduces the spontaneous firing of inhibitory neurons (marked by decreasing alpha-line in Fig. 2). This condition should normally lead to increased neuronal activity with synchronization in the gamma frequency range ("release of inhibition"). However, this *augmenting tendency* is counteracted by a *reducing tendency*, as the deafferentation not only hyperpolarizes the InhIn but also the ExPy. This is shown as an increasing "hypoactivation" line in Fig. 2. Due to the excitatory inputs of neurons at the audiometric edge, the increasing hypoactivation or release of inhibition are supposed to be smooth. In a certain region of the tonotopic map,

an increase of synchronized neuronal activity will emerge where these two opposing tendencies cross. This represents a region where a release of inhibition is strong enough to enhance activity of the ExPy and the hypoactivation that occurs at the same time is not strong enough to make firing of ExPy improbable. *In our view, the locally accentuated gamma activation constitutes the neuronal correlate of the tinnitus perception.*

This model is able to explain several empirical findings and observations: The model predicts that the enhanced gamma activity is not located at the audiometric edge but within the frequency range of hearing loss, as reported by Norena and Eggermont (2003). The model also explains why only parts of the region that is deprived of input synchronize, which is in keeping with the observation that the majority of the participants in tinnitus studies report a tonal sensation (i.e., they say that their perception has a distinct pitch even though they may have problems when it comes to matching the frequency of their tinnitus to a tone). Finally, the model emphasizes the importance of top-down mechanisms, which influence the subjective loudness of tinnitus by modulating neuronal activity in the auditory cortex through higher structures such as emotion and attention controlling systems. The model assumes that the descending (top-down) influence is exerted largely via inhibitory connections to InhIn. Periods of focused attention toward the tinnitus sound lead to a further alpha desynchronization and gamma synchronization on an electrophysiological level (Bauer et al., 2006). The overall spectral changes associated with tinnitus become more pronounced aggravating the distress on a subjective and behavioral level.

Certainly this model needs to be refined. Yet it creates some testable hypotheses that we hope will lead to further neuroscience research of tinnitus.

Abbreviations

CF	characteristic frequency
EEG	electroencephalography
ExPy	excitatory pyramidal neurons
InhIn	inhibitory interneurons
LFP	local field potential

LTP	long-term potentiation
LTS	low-threshold spike
MEG	magnetencephalography
RI	residual-inhibition
TEN	threshold equalizing noise

Acknowledgments

Our work on tinnitus is funded by the Deutsche Forschungsgemeinschaft and the Tinnitus Research Initiative. We thank Winfried Schlee and Olivier Bertrand for useful discussions that helped to form the ideas formulated here.

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CHAPTER 7

Applications of magnetic resonance spectroscopy to tinnitus research: initial data, current issues, and future perspectives

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Abstract: Conducting tinnitus research on humans poses challenges for investigators because of its subjective nature, the complexities involved in establishing underlying generator sites, the diversity of potential causes, and the inherent difficulties in dissociating reactive changes in the central nervous system (CNS), secondary to peripheral hearing loss, from those effects that may be due to tinnitus. One area of considerable interest concerns biomarker development, particularly in the areas of metabolism and biochemistry. Establishing a biomarker or a profile of metabolic and neurobiochemical constituents of tinnitus-related activity within the CNS could be of considerable importance for understanding the fundamental properties of this disorder. Therefore, in an effort to gain greater insight into mechanisms of tinnitus, magnetic resonance spectroscopy (MRS) is being proposed as one of the several tools that can address pertinent issues. Apart from its long-standing use in analytical chemistry and physics, MRS is also being applied with greater frequency in the neurosciences to gain insight into human brain function under normal and pathological states. By considering the history of this method and advances made to date, MRS has the potential to: (1) identify unique in vivo metabolic and neurobiochemical biomarkers associated with tinnitus in specific regions of the CNS, (2) clarify and track disease pathogenesis, (3) monitor short and long-term treatment effects, and (4) serve as a tool in testing of drugs that may be used in treatment of tinnitus.

Keywords: tinnitus; magnetic resonance spectroscopy; magnetic resonance imaging; voxel; LCModel; metabolites

Introduction

Applying available technology and developing it for specific needs, is an efficient way to provide solutions to current day problems and at the same time advance science. This conceptual and

philosophical framework forms the basis of this chapter and introduces magnetic resonance spectroscopy (MRS) to the study of tinnitus and its pathophysiology. Herein, we describe the application, development, and preliminary data derived from MRS, which is inherently targeted with respect to the many applications it has to auditory neuroscience research in general (e.g., Richards et al., 1997; Cacace et al., 2000; Aydin et al., 2005;

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Gallinat et al., 2006; Sörös et al., 2006) and to tinnitus research in particular.

Ever since Felix Bloch and Edward Purcell shared the 1952 Nobel Prize in Physics for discovering that magnetic resonances could be measured in liquid and solid materials, the evolution of this methodology and the contributions it has made to science (physics, chemistry, biology) and medicine has been nothing less than extraordinary. The initial experiments, performed independently by research groups at Stanford and Harvard Universities, found that when hydrogen atoms were placed in a static magnetic field and radio-frequency (RF) energy fields were applied, energy was absorbed by protons within the RF bandwidth and then re-emitted when nuclei relaxed back to their original state¹ (Bloch et al., 1946; Purcell et al., 1946). Consequently, if energy transfer from one system to another was due to a coincidence in their characteristic frequencies that resulted in magnetic moments flipping from lower to higher energy states, then the nuclei were described as being “*in resonance*”. These elegant experiments formed the basis of nuclear MRS and this methodology evolved into an important analytical tool to study the underlying structure and chemical composition of condensed matter. In terms of its relevance to current applications, the choice by the early pioneers to study the hydrogen atom found in water molecules has two important features: it is the most abundant element in the human body and the single proton found in this nucleus emits a strong signal (Weiner and Hetherington, 1989).

In terms of the historical time line, MRS predated imaging applications by over two decades. However, imaging was crucial to the development of MRS for in vivo human applications because regions-of-interest (ROI) within the central nervous system (CNS) needed to be precisely defined so that biochemical information from tissue could be extracted with a high degree of specificity. In this context, Lauterbur (1973) was credited for describing the method used to reconstruct the spatial MR properties of an object in two or three

dimensions (initially called zeugmatography). This important technical achievement led to the first cross-sectional image of a human finger in vivo (Mansfield and Maudsley, 1976a,b)² and thus set the stage for today’s innovations in magnetic resonance imaging (MRI). While these examples highlight a few prominent historic details, the interested reader is directed elsewhere for a more comprehensive overview (see Mattson and Simon, 1996). Nevertheless, to put these imaging accomplishments in perspective, some notable applications in their current form include: the reconstruction of three-dimensional high-resolution displays of human anatomy (brain and body), the development of novel experimental protocols that allow for the dynamic assessment of brain function during sensory, motor, and cognitive activations (functional MRI, fMRI),³ and the ability to extract and display white matter tracks in the brain (diffusion tensor imaging, DTI), under both normal and diseased states. Given present trends towards increasing the magnetic field strength of new generation scanners, coupled with advances in digital signal processing, and the ever-rapid gains in computing power, further advancements are looming on the horizon.

Functional and structural MRI studies are research endeavors on tinnitus. Because these areas are safe, vibrant, and growing in appeal, the momentum which has captured unique single-subject aspects of tinnitus-related activity in the past decade has served as a precursor to the

²Paul Lauterbur at the University of Illinois, Urbana, was awarded the Nobel Prize for Physiology or Medicine in 2003 for his discoveries in magnetic resonance imaging. He shared the prize with Sir Peter Mansfield, a physicist at the University of Nottingham in England, who is credited with further developing this technology.

³Within this time frame, there was a transition in descriptive language from the semantically precise terminology “nuclear magnetic resonance” (NMR) imaging to the more congenial and benign expression “magnetic resonance imaging” (MRI), which is now part of the common language. Apparently, the term “nuclear” conveyed negative and intimidating connotations to the lay public (i.e., nuclear reaction, nuclear bomb, nuclear war, etc.) rather than the fact that this term actually referred to the “nucleus” of atoms (i.e., the very small dense region of positive charge, in its centre of the atom consisting of protons and neutrons).

¹Purcell and colleagues used a block of paraffin wax as their hydrogen source, whereas Bloch and colleagues used water within a glass sphere.

development and refinement of magnetic resonance (MR) methods and models for use in group studies (e.g., [Cacace et al., 1995, 1999](#); [Melcher et al., 2000](#); [Muhlau et al., 2006](#); [May et al., 2007](#)).

Magnetic resonance spectroscopy (the first-order extension of Purcell and Bloch's groundbreaking discovery) is an imaging tool that falls between the domains of neurochemistry and functional imaging. Indeed, it is becoming established as an important tool in the neurosciences to study brain function under normal and pathological states (e.g., [Hollingsworth et al., 2006](#); [Talos et al., 2006](#); [Minati et al., 2007](#)). Both MRS and fMRI have additional applications geared towards improving specificity in the testing new drugs ([Borsook et al., 2006](#); [Mason and Krystal, 2006](#)). The extension and use of MRS to tinnitus research is intuitively obvious based on its potential to provide metabolic and neurobiochemical profiles of human brain tissue in a non-invasive manner. In contrast to other human imaging modalities like positron emission tomography (PET), where radiopharmaceuticals are needed and where safety issues associated with even low-level exposure is an inherent concern ([Strzelczyk et al., 2006, 2007](#)), MRS has clear advantages and growing support, particularly with respect to repeated measures experimental designs. Indeed, ^1H MRS is well positioned to serve as a probe of cerebral function and, if successful, will develop into a method of considerable value in tinnitus research.

Proton MRS of the brain can be applied in a number of different ways, including the use of single-voxel techniques, multi-voxel techniques, and spectroscopic imaging.⁴ Single-voxel MRS provides a profile of metabolites within a specific ROI in different volumes of brain or other types of tissue. Multi-voxel techniques provide biochemical information about multiple, small contiguous volumes, also focused within a specific ROI. Spectroscopic imaging takes single or multiple metabolite(s) of interest and plots their spatial distribution within the entire brain. We used single-voxel ^1H MRS to study the neurobiochemical profiles of the auditory cortical regions of the adult

human brain within the left- and right-temporal lobes. In the present study we targeted metabolites of *N*-acetyl aspartate (NAA), creatine (Cr), choline (Cho), glutamate (Glu), and gamma-aminobutyric acid (GABA). Precisely how these measures may be related to tinnitus (with or without hearing loss) remains to be determined.

Excitatory and inhibitory neurotransmitters like Glu and GABA are of considerable interest to tinnitus research. Under conditions where excitatory neurotransmitters might be up-regulated or where inhibitory neurotransmitters down-regulated (i.e., following otological disease states, ischemia and reperfusion, following administration of ototoxic pharmaceuticals, after noise-induced hearing loss, as a result of peripheral deafferentation, etc.), the delicate balance between excitation and inhibition can be altered and different scenarios can be conceptualized for initiating tinnitus at both peripheral and central levels (e.g., [Salah and Nodar, 2001](#); [Nuttall et al., 2004](#); [Mazurek et al., 2006](#); [Brozowski et al., 2007](#)).

As a precursor to the use of MRI and MRS techniques to study individuals with tinnitus, we performed these measures in normal-hearing individuals who did not have tinnitus. The purpose was to establish a library of chemical properties within the left and right hemispheres of the human brain. A third site, within the left-occipital lobe, was also evaluated as a control area but these data will not be reported here. In this data set, we were interested in ascertaining whether age, gender, and hemisphere played a role.

Methods

Experimental design and participants

Magnetic resonance imaging and MRS were obtained in 60 normal-hearing adults *without* tinnitus. As part of our inclusion criteria, all participants were required to have a negative history of otological, neurological, or psychiatric diseases, the absence of tinnitus, and pure tone hearing sensitivity less than or equal to 25 dB HL at octave frequencies from 0.25 to 4.0 kHz, bilaterally. We considered pure tone thresholds in this decibel

⁴A voxel is a digital measure of volume analogous to a cube within a three-dimensional grid.

range to be within normal limits. Lastly, all individuals that participated in the MRS experiment were required to complete and pass a detailed MR safety questionnaire prior to being scanned.

Two groups of individuals participated: Group 1, $n = 30$, included individuals less than or equal to 50 years of age (15 males, 15 females); Group 2, $n = 30$, included individuals greater than 50 years of age (15 males, 15 females). Handedness was evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971); associated hair whorl features were also noted when possible (Klar, 2003). Five individuals (three females; two males) were excluded from the study either because they were unable to remain in the gantry of the scanner for any prolonged period of time or because they refused to enter the scanner due to apparent fear of enclosed spaces (claustrophobia). One individual (female) did not fit into the bore of the magnetic due to obesity.

This study was approved by the Institutional Review Board (IRB) of the Albany Medical College and was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, US 21CFR Part 50 (Protection of Human Subjects, and Part 56 — Institutional Review Boards), and pursuant to state and federal Health Insurance Portability and Accountability Act (HIPAA) provisions (Public Law 104–191, 1996). Written informed consent was obtained from all participants before any specific procedures were carried out. In addition, applicable privacy requirements were met by having individuals sign a separate HIPAA research authorization, which is part of local policy at Albany Medical College. Participants were given a financial stipend for their participation.

MRI and MRS procedures

Magnetic resonance imaging of the brain was obtained using a high-field 3 Tesla (T) MR scanner (General Electric Signa, long bore device) with a standard quadrature head coil. After completing the informed consent process, passing an MR safety questionnaire and following a detailed discussion of the imaging protocol with the MR technologist, each participant was placed in the midline of the scanner lying in a supine position

with soft foam pads comfortably placed against each side of the head to minimize movement. Compressible foam earplugs (E-A-R, Aearo Company, Indianapolis, IN) were provided to reduce the effect of scanner noise.

Anatomical localizer image

A 3-D, spoiled gradient recalled acquisition (SPGR) T1 weighted pulse sequence (field-of-view, FOV, 22 cm; slice thickness = 2 mm; matrix, 256×125 , NEX = 1; flip angle 15° , echo time TE = 5.2 ms; inversion time TI = 300 ms, repetition time TR 12 ms) was used to obtain anatomical images. Data acquisition time for this pulse sequence lasted ~ 5 min. After images were acquired, scans were reviewed to rule out any morphological abnormalities or disorders that would exclude the individuals from participating in the study.

The MRS protocol used single voxel point-resolved spectroscopy (PRESS) 2D-J sequence similar to that used by others (Levy and Hallett, 2002; Levy et al., 2002; Levy and Henkin, 2004). While the current PRESS sequence uses the following parameters: (ROI 2 cm,³ flip angle = 90° , TE = 35 ms, TR = 2000 ms, thickness/sp = 19.6 cm, FOV = 22.22 cm, NEX = 2), modifications or alternative protocols may be necessary to enhance detection of GABA or other inhibitory neurotransmitters like glycine in future studies. Voxel size approximated $2 \times 2 \times 2$ cm (~ 8 cm³). Data acquisition time for this pulse sequence lasted ~ 8 min and locations for study included left- and right-auditory cortical areas and a control site in the left-occipital lobe.

Voxel placements for MRS were performed manually after the high-resolution anatomical images were acquired. We developed an informal, albeit useful method for gathering information that would include important anatomical landmarks such as Heschl's gyrus and surrounding areas (Hackett et al., 2001; Sweet et al., 2005). To help identify auditory cortical areas, we began by defining its most anterior aspect by identifying the central sulcus from sagittal and coronal of the SPGR images. Using the scanned images, we followed the central sulcus to where it approaches

and/or intersects with the Sylvian fissure. To a first approximation, this intersection point was used as a simple way to identify the most anterior segment of auditory cortex of each hemisphere. We then followed this point-of-intersection posteriorly by sequentially viewing coronal slices of the brain, so as to ensure capture of auditory cortical areas of interest, most notably Heschl's gyrus, planum temporale, and surrounding areas. With the voxel placed in the ROI, we attempted to maximize gray and white matter components, minimize areas of cerebrospinal fluid, and avoid lateral aspects of the skull, which might induce artifacts within the voxel. Then, this area was imaged using PRESS-J pulse sequence and stored as a file for later off-line data analysis. The LCModel (Provencher, 1993, 2001), a commercially available and licensed software tool, was used for MRS quantification. It is noteworthy that there are different ways to quantify and portray MRS data (i.e., absolute concentrations vs. ratio values) with the acknowledgement that each methodology has limitations and potential for error. For purposes of this experiment, we chose to use absolute concentrations derived from the LCModel.

MRS analysis

For each ROI in the left- and right-temporal lobes, the LCModel, Version 6.1 running on a LINUX workstation (Dell, Precision 670), was used to quantify metabolites based on the maximum likelihood method and Cramer-Rao Lower Bounds. Figure 1 provides the general features of our imaging protocol. The top portion of the figure shows a coronal MRI slice of the brain with voxel placement (white cube) within the right hemisphere for MRS. The bottom portion of the figure shows the output of the LCModel and the corresponding metabolic spectra.

Statistical analysis

A three-way analysis-of-variance (ANOVA) with repeated measures was used to evaluate effects of age (participants younger than or equal to 50 years vs. participants older than 50 years), gender

(male vs. female groups), and hemisphere (left vs. right) for each of the neurobiochemical constituents studied (Glu, NAA, Cre, Cho, and GABA). Pure tone audiometric data were also evaluated with ANOVA to assess the effects of age, gender, frequency, and ear.

Results

All participants required two visits: one for audiological evaluation and the second for MRI/MRS testing. Our cohort was well matched with respect to age (Fig. 2) and pure tone hearing thresholds (Fig. 3). All participants had pure tone thresholds less than or equal to 25 dB HL at octave frequencies from 0.25 to 4.0 kHz, bilaterally. While hearing was in the normal range bilaterally, ANOVA showed a significant age \times gender \times ear interaction ($F = 5.79$, $p < 0.02$) indicating that older male participants had higher pure tone thresholds in the left than in the right ear. Answers given on the Edinburgh Handedness Inventory showed that 93% of the participants were right handed.

Analysis of the obtained MRS showed consistent patterns of metabolic peak concentrations in all participants and for each hemisphere evaluated. Table 1 summarizes the statistical main effects of age, gender, and hemisphere, which emerged from the ANOVA for each of the metabolites under consideration. In this analysis, there were no higher-level statistical interactions for any of the variables under consideration. The main effect of age was significant for Glu and NAA, and was characterized by higher concentrations in individuals younger than 50 years than what was found in individuals older than 50 years. The main effect of gender was significant for Glu, NAA, and Cre and was characterized by higher concentrations in males than in females. The main effect of hemisphere was significant for Glu, NAA, Cre, Cho, and GABA, with higher concentrations found within the left than the right hemisphere (see Figs. 4–6).

Discussion

While preliminary in nature, this study suggests that age, gender, and hemisphere are potential

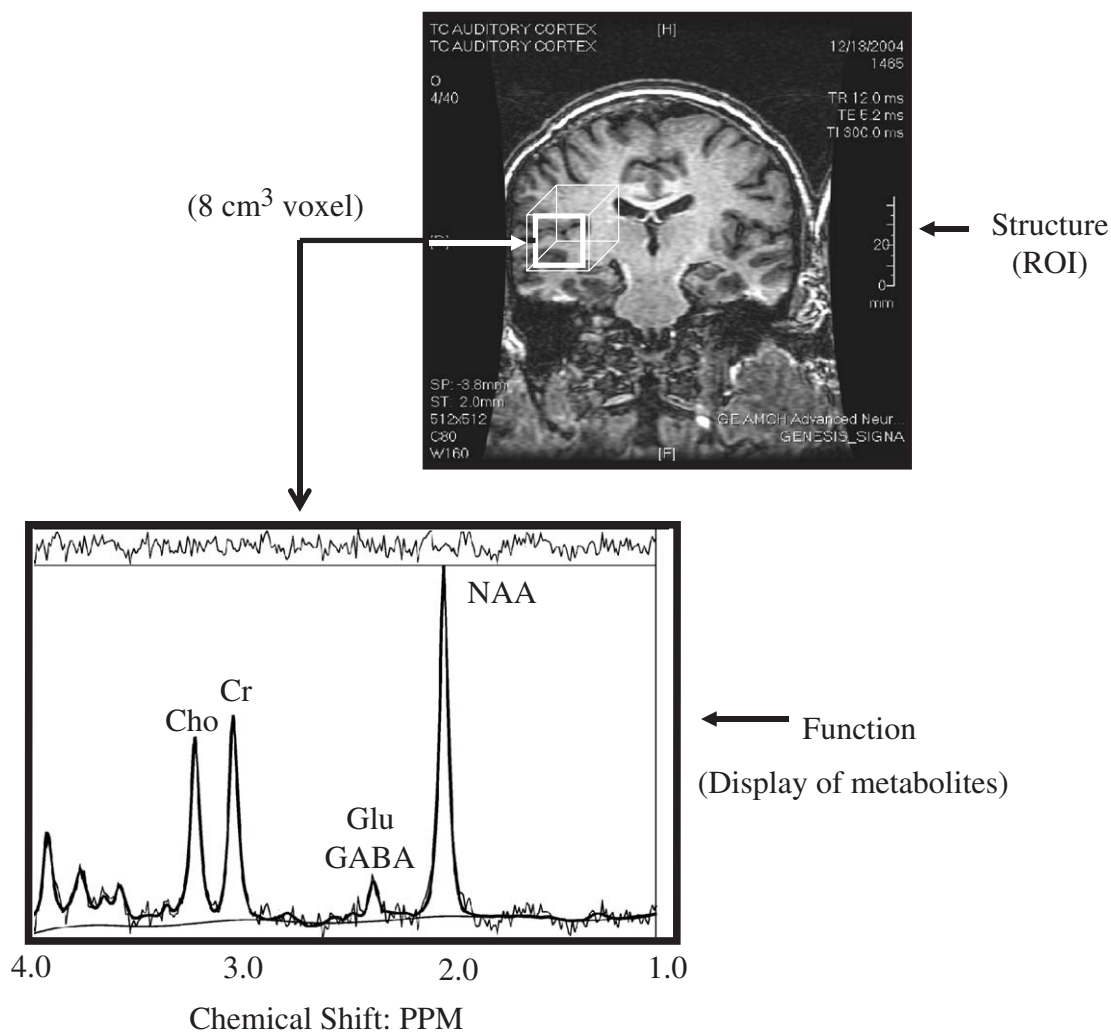


Fig. 1. (Top) Coronal MRI slice of the brain; the white cube demarcates the area of auditory cortex to be imaged using MRS from the right hemisphere of the brain. (Bottom) Shows the output of the LCMoel including the metabolite spectra from the auditory cortex in the temporal lobe of the right hemisphere.

factors that should be considered for future investigations. When data were collapsed across gender and hemisphere, significant age effects were noted for Glu and NAA indicating that approximately 12% higher concentrations of these metabolites were present in the younger than in the older age groups (Fig. 4). A recent imaging study has shown a loss of gray matter across the cortical surface at an annual rate of $0.91 \pm 0.92\%$ per year (left hemisphere $1.16 \pm 1.41\%$ per year; right hemisphere

$0.67 \pm 1.25\%$ per year) with few regions exceeding 1% annually (Thompson et al., 2003). These changes were most likely due to cell shrinkage (Terry et al., 1987). Other neuroanatomical changes such as reduced dendritic extent and synaptic loss have been found to occur in atrophic or disease brains (i.e., Uylings and de Brabander, 2002). Using 0.91% per year, as an estimate of gray matter loss, the average reduction in metabolite concentration we observed for Glu and NAA

was less than the estimated gray matter loss (Glu, 20.8%; NAA, 24.3%).

When data were collapsed across age and hemisphere, statistically significant gender effects were observed for Glu, NAA, and Cre. These findings were greater in males than females (Fig. 5). Several factors may be related to these biochemical observations. For example, Jäncke et al. (1994) reported that the planum temporale had greater asymmetries in males vs. females. Using voxel-based morphometry, Good et al. (2001) also found significant asymmetries in the temporal lobes whereby Heschl's gyrus and planum temporale had greater leftward asymmetry in males than in females. This result was consistent with the idea that brain structure is more lateralized in males than in females (e.g., Hiscock et al., 1994; Shaywitz et al., 1995; Narr et al., 2001; Sowell et al., 2002). However, when a ratio metric of metabolites to Cre

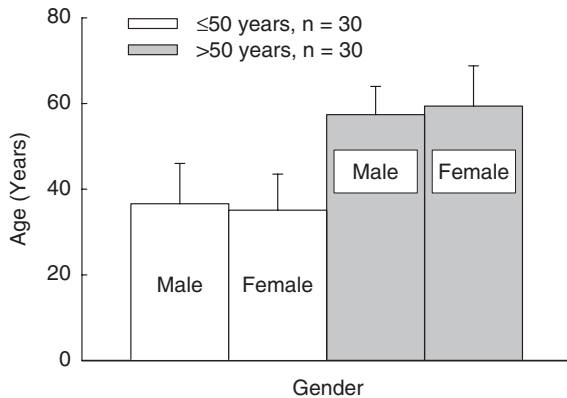


Fig. 2. Bar graphs showing age and gender matching in this cohort of 60 adults.

was used to express metabolite concentration magnitude in an area of the left-temporal lobe that was similar to the location used in the present investigation, gender effects were not observed for either NAA/Cre or Cho/Cre (Komoroski et al., 1999). However, their sample of male and female subjects (males, $n = 37$, ages 22–67 years; females, $n = 53$, ages 19–61 years), magnetic field strength

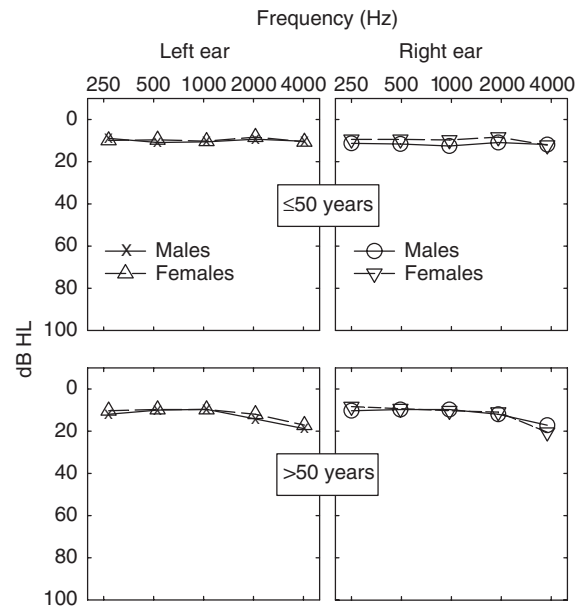


Fig. 3. (Top) Average pure tone audiograms from individuals ≤ 50 years of age. Left column represents male and female data for the left ear; right column represents male and female data for the right ear. (Bottom) Average pure tone audiograms from individuals > 50 years of age. Left column represents male and female data for the left ear; right column represents male and female data for the right ear.

Table 1. (Y-axis) Dependent variables were rank ordered in terms of their estimated concentration gradients from highest to lowest: glutamate (Glu), *N*-acetyl-aspartate (NAA), creatine (Cre), and gamma-aminobutyric (GABA)

	Dependent variables		
	Age	Gender	Hemisphere
Metabolites			
Glu	$F = 8.75, p < 0.005$	$F = 10.27, p < 0.003$	$F = 34.09, p < 0.0001$
NAA	$F = 10.22, p < 0.003$	$F = 5.85, p < 0.02$	$F = 50.33, p < 0.0001$
Cre		$F = 18.92, p < 0.001$	$F = 80.00, p < 0.0001$
Cho			$F = 22.72, p < 0.0001$
GABA			$F = 4.05, p < 0.05$

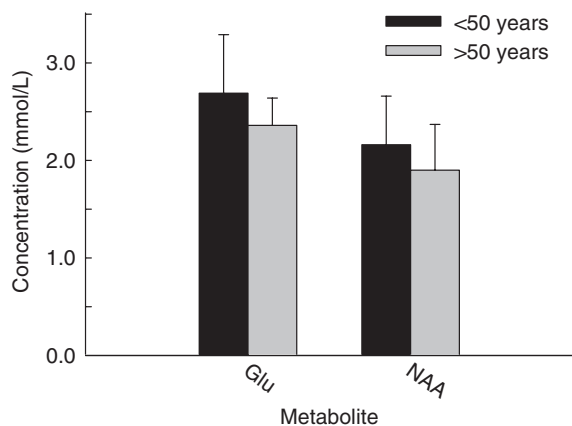


Fig. 4. Bar graphs showing main effect of age for Glu and NAA. As shown, greater concentration of each metabolite was found in the younger vs. older age group.

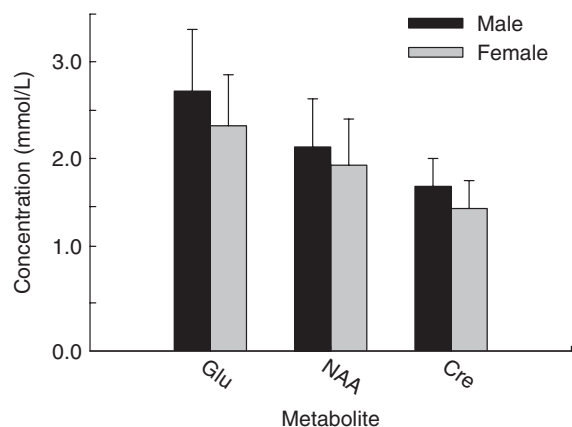


Fig. 5. Bar graphs showing main effect of gender for Glu, NAA, and Cre. As shown, greater concentration of each metabolite was found in male vs. female participants.

(1.5 T), and pulse sequence differed from ours. If a similar ratio scale was applied in our data and was subjected to ANOVA, gender differences also failed to reach significance (Glu, $F = 0.06$, $p > 0.82$; NAA, $F = 2.52$, $p > 0.11$; Cho, $F = 84$, $p > 0.35$). In this context, it would appear that the use of a ratio scale might not be optimum when applied to these data.

When the obtained data were collapsed across age and gender, significant hemisphere effects were observed for Glu, NAA, Cre, Cho, and GABA, with higher concentrations of metabolites

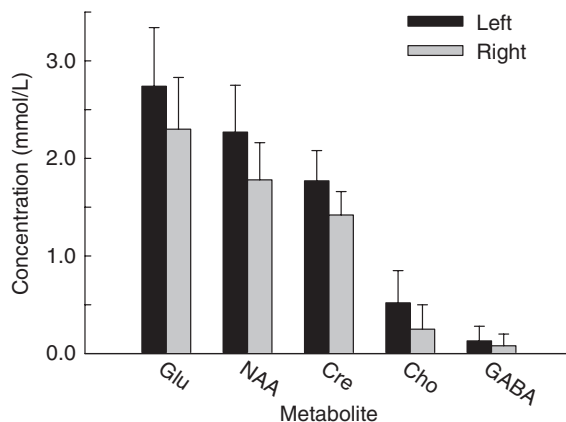


Fig. 6. Bar graphs showing main effect of hemisphere Glu, NAA, Cre, Cho, and GABA. As shown, greater concentration of each metabolite was found in the left vs. right hemisphere.

observed in the left than the right hemisphere (Fig. 5).⁵ Left–right brain asymmetries of auditory cortical areas of humans have been described especially with respect to anatomical differences in structures like the planum temporale, Heschl’s gyrus, and the Sylvian fissure and their relationship to language lateralization and handedness (e.g., Toga and Thompson, 2003; Dorsaint-Pierre et al., 2006). Imaging studies have also shown that Heschl’s gyrus and the Sylvian fissure were larger on the left side (Rademacher et al. 1993; Penhune et al., 1996). Additionally, Luders et al. (2006) found asymmetries in cortical thickness, which were most significant for left/right clusters located in the anterior temporal lobe and inferior, middle, and superior temporal gyrus. Cortical thickness is also related to intrinsic cellular characteristics such as packing density, myelination, cell size, and a number of cortical neurons (Kruggel et al., 2003; Eickhoff et al., 2005). As noted above, Good et al. (2001) found a left hemisphere asymmetry for Heschl’s gyrus and planum temporale that was greater for males than for females. Moreover,

⁵Because the concentrations of GABA were close to or in the noise floor, they are not considered reliable measures, even though they show the same pattern of hemispheric asymmetries as the other metabolites. This limitation is currently being pursued for future investigations by pulse sequence development, more sophisticated quantification methods and/or measurement of other inhibitory chemicals.

based on R1 longitudinal relaxation rates, a leftward bias towards gray matter myelination was also recognized in a small sample of adults without a history of neurological disorders or tinnitus (Sigalovsky et al., 2006).

Neurobiochemical asymmetries including those of the temporal lobe have received limited attention. A study of 28 right-handed healthy adults (12 male, 16 female), in which single-voxel MRS was localized to a mesial temporal lobe location (hippocampus), larger NAA/Cho, NAA/Cr, and Cho/Cr ratios were found in the left than the right hemisphere (Bernard et al., 1996). In another study of 100 normal male volunteers (20–30 years) without known neurological deficits, larger NAA/Cr, NAA/Cho, and Cho/Cr ratios were also found in left vs. right temporal lobes hemispheres (Jayasundar and Raghunathan, 1997). In a later study, using absolute metabolite concentrations derived from the LCModel, similar effects were observed (Jayasundar, 2002).

Conclusion

The preliminary results of this study show that single-voxel MRS from auditory cortical areas of the left- and right-temporal lobes produced consistent data within and across participants. Both MRI and MRS procedures were well tolerated by individuals of all ages and no adverse effects were reported. The consistency of the results (Figs. 4–6) may be attributed to the age- and gender-matched cohort without peripheral hearing loss or history of otological, neurological, or psychiatric diseases.

In summary, MRS represents a powerful imaging tool that may contribute to understanding the underlying mechanisms of tinnitus and provide a means to monitor treatments.

Abbreviations

ANOVA	analysis-of-variance
Cho	choline
CNS	central nervous system
Cre	creatine
DTI	diffusion tensor imaging
FOV	field-of-view

fMRI	functional magnetic resonance imaging
GABA	gamma amino butyric acid
GLU	glutamate
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NAA	<i>N</i> -acetyl-aspartate
PET	positron emission tomography
PRESS	point-resolved spectroscopy
RF	radiofrequency
ROI	region-of-interest
SPGR	spoiled gradient recalled acquisition
T	tesla

Acknowledgments

We thank Dr. Dennis J. McFarland for assistance with the statistical analysis, Mr. John Cowan for excellent technical assistance with MR imaging, and Dr. Earl Zimmerman for his support. This work was generously supported by a grant from the American Tinnitus Association. Portions of this work were presented in as magazine article for *Tinnitus Today*, a periodical of this organization.

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CHAPTER 8

Functional imaging of chronic tinnitus: the use of positron emission tomography

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Abstract: Recent advances in functional imaging have opened new possibilities for understanding tinnitus. Especially, positron emission tomography (PET) has been increasingly used in the last two decades to identify cortical networks, which are involved in the generation of various forms of chronic tinnitus. PET studies have confirmed that the anatomical location of the anomalies that cause many forms of tinnitus are regions of the brain that are normally involved in auditory processing as well as regions engaged in emotional processing. These findings have contributed to the development of new more causally oriented treatment strategies. In particular, identification of increased activity of the auditory cortex by PET has prompted the use of focal brain stimulation techniques such as electrical or transcranial magnetic stimulation in treatment of tinnitus. PET studies that map distinct neurochemical pathways and receptors by the use of specific ligands may in the future provide new possibilities for pharmacologically based treatment of some forms of tinnitus.

Keywords: positron emission tomography; tinnitus; functional imaging; neuroplasticity; diagnostic; categorization

Introduction

It has become widely accepted that maladaptive changes of central information processing are involved in generating the neural activity that causes the perception of many forms of tinnitus (Møller, 2003). Functional imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have contributed to identify the anatomical location of the physiological abnormalities that cause some forms of tinnitus.

PET makes use of a radioactive tracer to identify the anatomical location of indicators of neural activity such as blood flow or glucose metabolism. By using different tracers PET can show where neural activity *changes* such as in response to a change in tinnitus or detect the spatial pattern of steady-state brain activity.

fMRI is usually less expensive and easier to perform while PET retains unique advantages in studies of auditory processing. While fMRI machines produce considerable noise (up to 130 dB) which is a disadvantage in auditory studies PET equipment produces almost no noise (Kim et al., 2000; Johnsrude et al., 2002). In contrast to fMRI, PET makes it possible to study individuals with cochlear implants or other kinds of implanted

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electrodes. PET is also much less sensitive to small movements, such as those from arterial pulsations in the brainstem.

Different PET-applications

In general, PET studies in tinnitus patients have been performed in two different ways. One approach has made use of the fact that oral-facial movements can modulate some forms of tinnitus, change in eye-positions, cutaneous stimulation or administration of lidocaine (Lockwood et al., 1998, 2001; Giraud et al., 1999; Mirz et al., 1999; Reyes et al., 2002). When such interventions were used to alter the loudness of tinnitus, corresponding changes in cortical activity were detected by PET that uses water labeled with radioactive oxygen ($[^{15}\text{O}]\text{-H}_2\text{O}$ PET) to detect changes in regional cerebral blood flow (rCBF), which is regarded as a surrogate marker of neuronal activity.

Another approach uses $[^{18}\text{F}]\text{-deoxyglucose-PET}$ (FDG-PET). The use of radioactively labeled glucose makes it possible to measure steady-state metabolic activity in cortical areas, which in turn is an indicator of neuronal activity. This technique has been applied to individuals with tinnitus (Arnold et al., 1996; Wang et al., 2001; Langguth et al., 2006).

Studies using $[^{15}\text{O}]\text{-H}_2\text{O}$ PET

PET that uses $[^{15}\text{O}]\text{-H}_2\text{O}$ has been applied to subgroups of individuals with tinnitus in whom the tinnitus can be modulated by specific interventions, such as eye movement (lateral gaze) (Giraud et al., 1999; Lockwood et al., 2001) orofacial movements (Lockwood et al., 1998), intravenous lidocaine (Mirz et al., 1999; Andersson et al., 2000; Reyes et al., 2002; Plewnia et al., 2006), auditory stimulation (Osaki et al., 2005), or cognitive distraction (Andersson et al., 2006).

Two PET studies took advantage of the fact that patients with this relatively rare condition can modulate their tinnitus by eye movements, a condition, which may occur after surgical operations in the cerebellopontine angle. Giraud et al. (1999) found that tinnitus sensation is associated with

an increase in rCBF bilaterally especially in auditory temporo-parietal association areas, whereas Lockwood et al. (2001) found signs of rCBF alterations in a large part of the frontal, parietal, and temporal cortex including the lateral pontine tegmentum and the primary auditory cortex (PAC). In individuals with gaze-evoked tinnitus worsening of tinnitus during lateral gaze was related to reduced inhibition of auditory cortex as compared to individuals who do not have that condition.

By investigating individuals with unilateral tinnitus who were able to alter tinnitus loudness in the scanner by oral-facial movements, the same research group found that neural activity increased and decreased in parallel to the reported loudness of tinnitus in areas adjacent to the *contralateral* auditory cortex. In contrast auditory stimulation in the same individuals resulted in *bilateral* activation of the auditory cortex suggesting that the abnormal neural activity that caused the sensation of tinnitus originated in the central auditory system rather than the cochlea (Lockwood et al., 1998). Cortical activation by tones was more widespread in individuals with tinnitus than in individuals without tinnitus. In individuals with tinnitus, auditory stimulation also resulted in activation of limbic structures indicating plastic changes of the auditory nervous system had occurred (also see Chapter 2).

Lidocaine administered intravenously can modulate tinnitus in many individuals (Melding et al., 1978; Mirz et al., 1999; Andersson et al., 2000; Reyes et al., 2002; Plewnia et al., 2006) (also see Chapters 24 and 25). Whereas most studies only included individuals where lidocaine decreased the tinnitus sensation, Reyes et al. (2002) also studied individuals who experienced an increase of their tinnitus after administration of lidocaine, to differentiate tinnitus-related effects from unspecific lidocaine effects. They found that the changes in the loudness of the tinnitus were associated with changes in the neural activity in the right auditory association cortex. These findings were confirmed and extended by the others. Thus Plewnia et al. (2006) identified a broad cortical network including the middle temporal gyrus, a brain region that involves auditory processing, as well as cortical areas involved in the integration (gyrus angularis)

and emotional validation (posterior cingulated cortex) of sensory stimuli.

Using [^{15}O]- H_2O PET in a study of eight individuals with tinnitus localized to the left ear ($n = 2$), both ears ($n = 4$), or in the head ($n = 2$). Andersson et al. (2006) showed that a cognitive task (silent backward counting) reduced both rCBF in auditory cortex and tinnitus loudness.

Taken together studies that have used PET that uses [^{15}O]- H_2O have consistently provided evidence of tinnitus-related increases of neural activity in auditory pathways and co-activation of non-auditory neural systems. However, the use of this technique depends on the ability to influence the intensity of the tinnitus by specific interventions. This is an obstacle in the use of this method for diagnostic purposes and it can only be used in subgroups of patients whose tinnitus can be modulated.

Studies using FDG–PET

By measuring regional glucose uptake, FDG–PET allows to assess metabolic activity, which in turn is a marker for neuronal steady-state activity. In contrast to [^{15}O]- H_2O PET the FDG–PET does not depend on the ability to change the tinnitus and it can therefore be used for diagnostic purpose in almost every tinnitus patient. This form of imaging was first used by Arnold et al. (1996) to detect changes of metabolic activity in tinnitus patients. Investigating patients with tinnitus localized to the left ear ($n = 6$), the right ear ($n = 2$), or in the head ($n = 2$) these investigators found asymmetric activation of the auditory cortices as compared to controls. Nine individuals with tinnitus had signs of significantly increased metabolic activity in the left PAC (Brodmann area 41), and one had increased activity in the right cortex. In an additional patient in whom the severity of the tinnitus changed, repeated PET scans showed that the metabolic activity of the left PAC changed in a similar way as the intensity of the tinnitus. These results were confirmed by one case report (Richter et al., 2006) and two studies involving larger sample sizes. These studies with 11 (Wang et al., 2001) and 20 participants (Langguth et al., 2006) also

found signs of asymmetric activation of the auditory cortices with increased metabolic activity, which was most pronounced in the left side. The finding that the degree of activity in the auditory cortex is correlated with treatment outcome of transcranial magnetic stimulation over this area (Langguth et al., 2006) emphasizes the pathophysiological relevance of increased auditory cortex activity.

The fact that all studies showed signs that the activation patterns is independent of the localization to which the tinnitus is referred (left or right ear, or the middle of the head), indicates that the localization to which the tinnitus is referred does not depend on how the auditory cortex is activated.

A major limitation of all published FDG–PET studies of tinnitus patients is that they are restricted to analysis of the auditory cortices.

PET for neurobiological subtyping of tinnitus patients

It is generally accepted that tinnitus is not a single entity but patients with tinnitus differ widely in the perceptual characteristics of their phantom sound, in their emotional reactions and in their response to specific treatments. These different forms of tinnitus may have distinct anatomical or physiological signatures. However most neuroimaging studies, which compared groups of individuals with tinnitus with controls have assumed a similar pathophysiology of different forms of tinnitus. However, since neuroimaging techniques allow differentiating between individuals with tinnitus and controls, they may also hold a potential for identifying specific abnormalities in the pattern of brain activity in clinically distinct subtypes of tinnitus.

It is well known that tinnitus is more frequent in men (Hoffman and Reed, 2004) and that perceptual and emotional characteristics of tinnitus differ between men and women (Hiller and Goebel, 2006). This in turn suggests that there may be gender-related differences in the neurobiological substrate of tinnitus. To test this hypothesis we studied the relationship between gender and steady-state regional brain activity in 83 patients

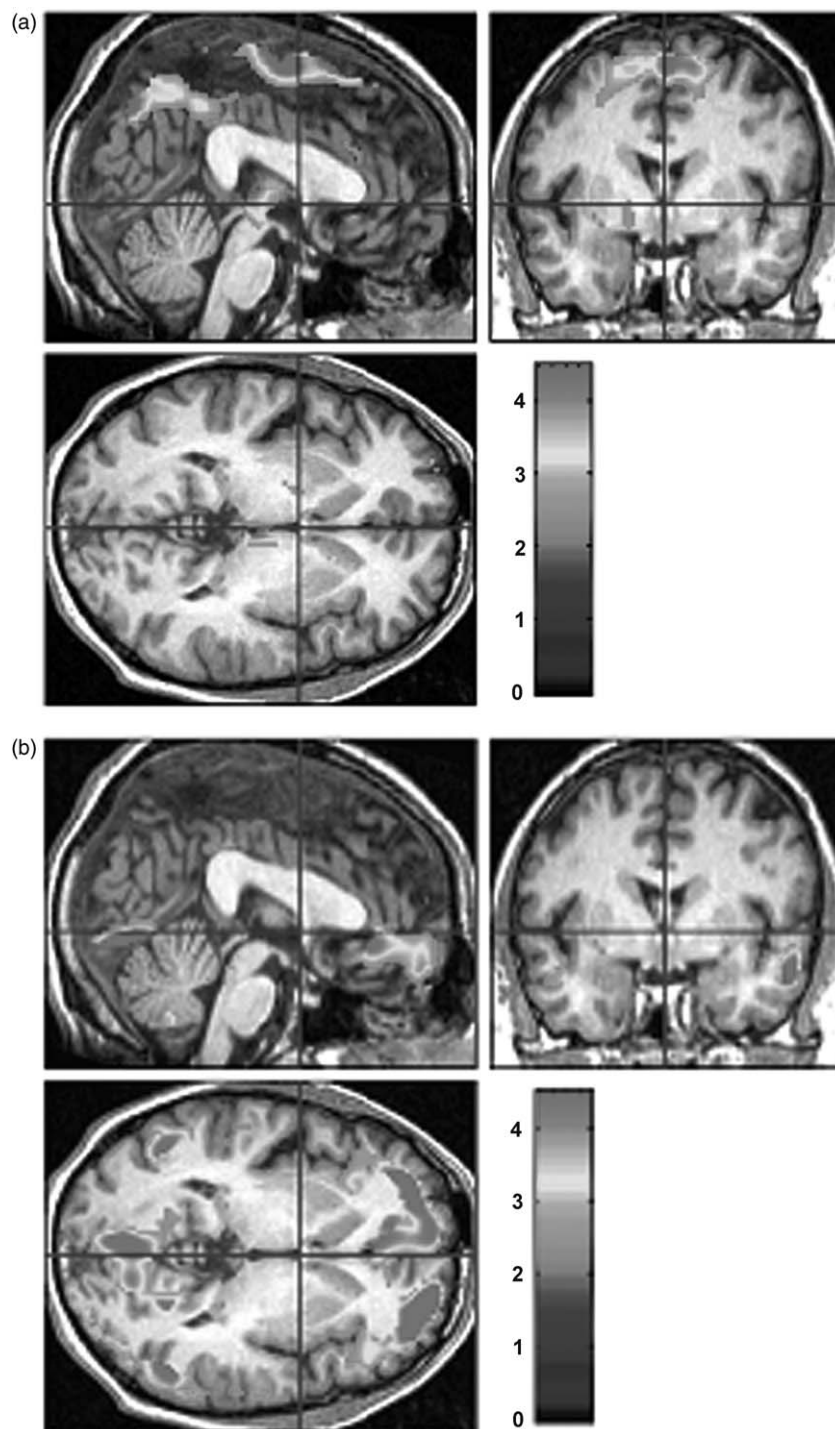


Fig. 1. (a) Increased metabolic activity preferentially in temporal and parietal brain regions in female tinnitus patients as compared to male tinnitus patients. (b) Increased metabolic activity in frontal and occipital regions in male tinnitus patients as compared to female tinnitus patients. (See Color Plate 8.1 in color plate section.)

(59 male and 24 female) with chronic tinnitus by using FDG-PET as previously described (Langguth et al., 2006). These patients were admitted to our tinnitus clinic, their age was 48.8 ± 12 years, tinnitus duration 6.5 ± 7 years, and tinnitus severity 36.8 ± 6.7 (Tinnitus Questionnaire, Goebel and Hiller, 1994).

The results of FDG-PET scans showed indications that female patients had significantly higher levels of activity in temporal and parietal brain areas than male patients (Fig. 1a). In contrast, male patients had signs of higher metabolic activity bilaterally in frontal and occipital regions as compared to female patients (Fig. 1b). These results underscore the neurobiological heterogeneity of chronic tinnitus and indicate the potential of neuroimaging methods to identify neurobiologic differences in clinically distinct subgroups of tinnitus. The results indicate that functional neuroimaging may be an effective method for identifying neurobiologically distinct subgroups of tinnitus.

Conclusion

PET studies have clearly demonstrated the involvement of the central nervous system in tinnitus and contributed much to our understanding of the pathophysiology of different forms of tinnitus. Such studies have shown signs of abnormalities in neuronal activity in many parts of the central nervous system indicating that the plastic changes that are associated with tinnitus are not limited to auditory brain regions but may also include brain areas involved in sensory integration, attentional processes, and emotional evaluation.

New treatment strategies evolved from the PET studies that demonstrated abnormal neuronal activity in the auditory cortex. Promising results from low-frequency transcranial magnetic stimulation have been obtained in several pilot studies (Eichhammer et al., 2003; Kleinjung et al., 2005; Plewnia et al., 2006, 2007) and from studies using direct electrical stimulation of the auditory cortex (De Ridder et al., 2004, 2006). The application of stimulation for treatment of tinnitus patients has been guided by functional imaging studies and applied to the areas that have shown signs of

increased metabolic activity in the auditory cortex. In addition to being used for guidance of treatment, preliminary findings suggest that the results of PET scanning may also serve as predictor of outcome of treatment (Langguth et al., 2006; Richter et al., 2006; Plewnia et al., 2007).

Further development of the use of PET scans may help develop pharmacologically based treatment strategies.

Abbreviations

dB	decibel
FDG	[¹⁸ F]-deoxyglucose
fMRI	functional magnetic resonance imaging
[¹⁵ O]-H ₂ O	water labeled with radioactive oxygen
PAC	primary auditory cortex
PET	positron emission tomography
rCBF	regional cerebral blood flow

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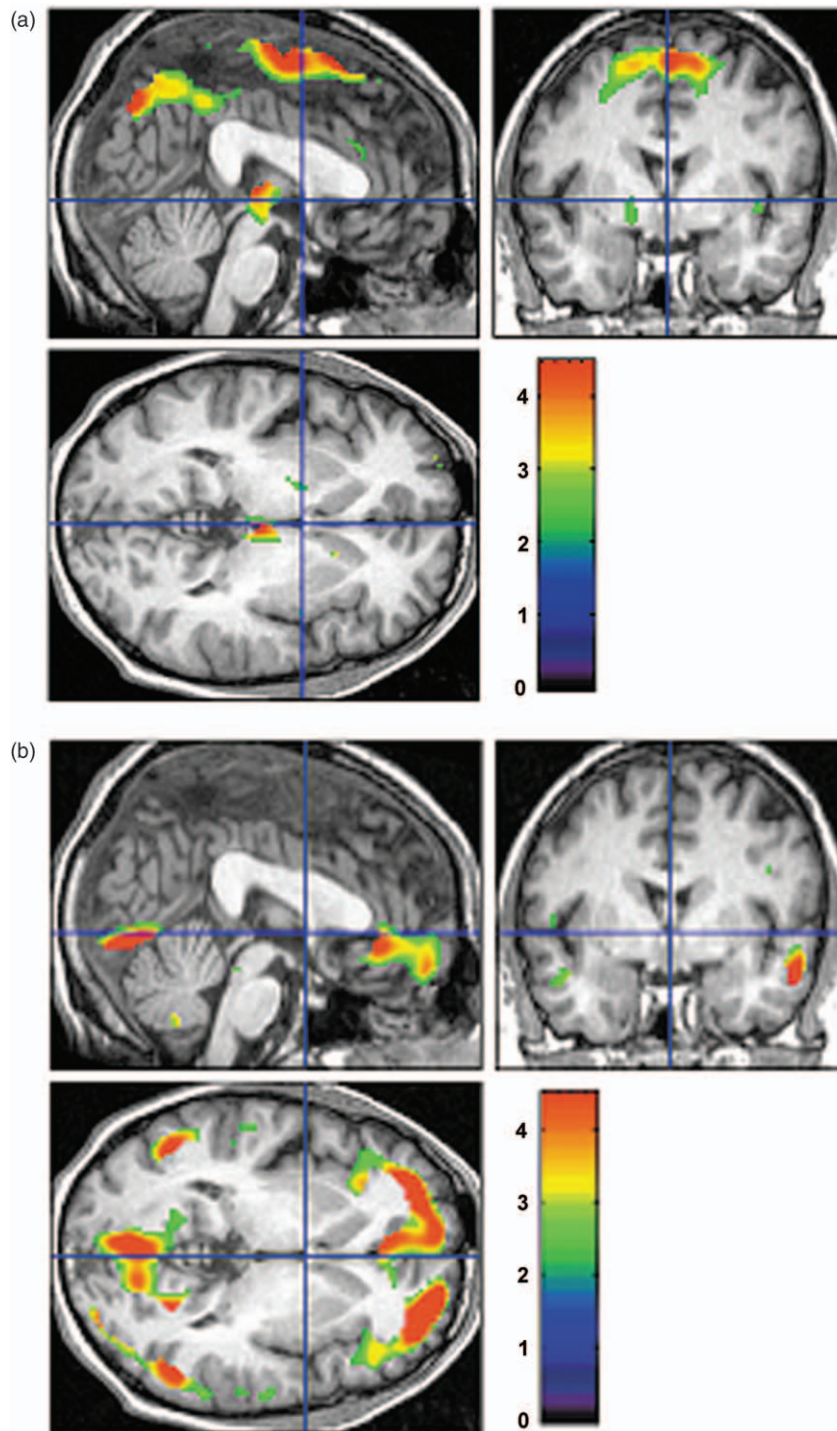


Plate 8.1. (a) Increased metabolic activity preferentially in temporal and parietal brain regions in female tinnitus patients as compared to male tinnitus patients. (b) Increased metabolic activity in frontal and occipital regions in male tinnitus patients as compared to female tinnitus patients. (For B/W version, see page 86 in the volume.)

CHAPTER 9

The dorsal cochlear nucleus as a contributor to tinnitus: mechanisms underlying the induction of hyperactivity

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Abstract: It has been hypothesized that tinnitus percepts may arise, in part, from increases in spontaneous neural activity in the central auditory system. The DCN is the lowest central auditory nucleus where this hyperactivity is observed, and it is most prominent following exposure to intense sound or ototoxic insult. Efforts to develop effective treatments for tinnitus will probably benefit from a better understanding of the mechanisms underlying the induction of hyperactivity in the DCN. This chapter will summarize the evidence linking tinnitus to altered activity in the DCN and review some of the likely mechanisms underlying the induction of hyperactivity following injury to the ear.

Keywords: tinnitus mechanisms; plasticity; dorsal cochlear nucleus; disinhibition; hyperactivity

Introduction

Over the past decade, an increasing number of animal models have been developed for the study of tinnitus mechanisms. Studies using these models have consistently demonstrated that agents which cause tinnitus in humans, such as sodium salicylate, noise and quinine, cause animals to experience tinnitus-like percepts (Jastreboff et al., 1988; Bauer et al., 1999; Brozoski et al., 2002; Heffner and Harrington, 2002; Guitton et al., 2003; Lobarinas et al., 2004). Although many changes in neuronal function have been observed in these animal models, the most frequently reported alteration is the condition of hyperactivity, characterized as an increase in spontaneous activity.

The evidence comes from studies using a variety of functional measures, such as single- and multi-unit recordings, c-fos immunocytochemistry and 2-deoxyglucose metabolic mapping (Jastreboff and Sasaki, 1986; Kaltenbach and McCaslin, 1996; Manabe et al., 1997; Eggermont and Kenmochi, 1998; Kaltenbach et al., 1998, 2002; Kimura and Eggermont, 1999; Kaltenbach and Afman, 2000; Komiya and Eggermont, 2000; Norena and Eggermont, 2003; Wallhauser-Franke et al., 2003; Ma et al., 2006). These studies have shown that the same tinnitus-inducing agents that cause animals to experience tinnitus also cause increases in spontaneous activity. This hyperactivity has been observed at several levels of the central auditory system, including the dorsal cochlear nucleus (DCN), the inferior colliculus (IC) and the auditory cortex (AC). The hypothesis that increased spontaneous activity represents a neural

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correlate of tinnitus has gained further strength from imaging studies showing hyperactivation of auditory areas in the brains of human subjects with tinnitus (Shulman, 1995; Arnold et al., 1996; Lockwood et al., 1998; Giraud et al., 1999; Andersson et al., 2000; Melcher et al., 2000; Mirz et al., 2000; Wang et al., 2000; Lockwood et al., 2001).

The DCN is the lowest level in the central auditory system where tinnitus-related hyperactivity has been observed (see reviews of Eggermont and Roberts, 2004; Kaltenbach et al., 2005). This structure has been implicated in localization of sounds in three-dimensional space, particularly in the vertical plane (Masterton et al., 1994; May, 2000); however, its connections with numerous other structures, both auditory and non-auditory, suggest that the DCN has additional functions (see Kaltenbach, 2006). Its involvement in tinnitus is of special interest for several reasons. First, because the DCN receives direct innervation from the auditory nerve, it is especially vulnerable to alterations of peripheral input, such as those that accompany cochlear injury resulting from exposure to tinnitus-inducing agents. Second, because its output is relayed to higher order auditory centers, it is in a position to influence, and perhaps even contribute to increases in, the levels of activity higher up in the auditory pathway. Third, it is a center of integration of different sensory modalities, and as such, provides cross-modal interactions that could offer avenues for treatment beyond the borders of the auditory system.

The DCN as a contributor to tinnitus

Numerous lines of evidence support the hypothesis that the DCN is an important contributor to tinnitus percepts. This evidence has recently been reviewed (Kaltenbach, 2006) and is summarized briefly here:

- (1) Direct electrical stimulation of the DCN has been reported to cause changes in the loudness of tinnitus (Soussi and Otto, 1994). The evidence comes from a study of 10 tinnitus patients with neurofibromatosis-2 (NF-2), each of whom received an auditory

brainstem implant (ABI) following bilateral acoustic neuroma (vestibular Schwannoma) surgery. In each patient, the ABI was implanted unilaterally on the surface of the DCN. The patients were asked to describe how their tinnitus percepts were affected during periods of ABI stimulation. Seven of the 10 patients reported a decrease in the loudness of their tinnitus during ABI stimulation, one reported an increase and two reported no change in their tinnitus. Some patients also reported changes in the pitch of their tinnitus or in the number of tinnitus sounds. However, the changes in tinnitus perception occurred only as long as the period of stimulation; there was no evidence of residual inhibition. The results of this study, though preliminary in nature, suggest that changes in tinnitus percepts are related to changes in the level of neural activity in the DCN. Since changes in tinnitus can also be elicited by stimulating the cochlea, the findings with the ABI stimulation may indicate that the DCN is a key part of a tinnitus-generating circuit that can be influenced by changes in the level of input from the auditory periphery.

- (2) Agents that cause tinnitus in humans also cause increases in spontaneous neural activity in the DCN of animals. This condition of hyperactivity, observed at both multi- (Fig. 1) and single-unit levels, occurs following either noise or ototoxic drug exposure, and has been demonstrated in several species, including hamsters (Kaltenbach and McCaslin, 1996; Kaltenbach et al., 1998, 2000, 2002, 2005), rats (Zhang and Kaltenbach, 1998), guinea pigs (Imig and Durham, 2005), mice (Kaltenbach et al., 2001), chinchillas (Brozoski et al., 2002) and gerbils (Wallhausser-Franke et al., 2003). This suggests that noise-induced hyperactivity in the DCN is an across-species phenomenon, although it has not yet been reproduced in brain slices (Chang et al., 2002) or in decerebrate animals (Ma and Young, 2006).
- (3) The hyperactivity induced in the DCN by intense sound exposure resembles the

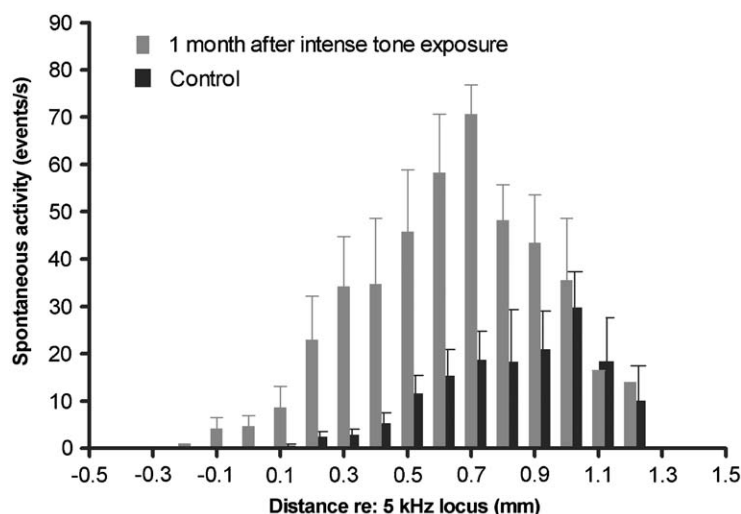


Fig. 1. Comparison of the levels of DCN spontaneous activity recorded in two groups of animals, one exposed to an intense (127 dB SPL) 10 kHz tone for 4 h (gray bars), the other serving as unexposed control animals (black bars). Mean activity is plotted for each group as a function of distance along the medial-lateral (tonotopic) axis of the DCN. Points along the X-axis represent distances from the lateral part of the DCN. The data show consistently higher levels of mean spontaneous activity (hyperactivity) in exposed animals relative to those of controls.

increases in activity evoked in the DCN of normal animals during moderate sound stimulation. For example, the distribution of hyperactivity across the tonotopic range displays a profile with a distinct peak. This profile is similar to what is observed in the DCN during stimulation with a moderate level 10 kHz tone (Kaltenbach and Afman, 2000). This similarity suggests that noise-induced hyperactivity in the DCN carries a place code for a tonal stimulus, which corresponds to the typical tonal character of tinnitus.

- (4) DCN hyperactivity displays several features that are in line with the psychoacoustic features of tinnitus. For example, although tinnitus usually has a distinct pitch, pitch matching studies have shown that tinnitus has a spectral profile more like that of a narrow band of noise (Norena et al., 2002). Similarly, the tonotopic spectrum of DCN hyperactivity is more like the profile of activity evoked by a narrow band of noise than by a pure tone (Kaltenbach and Afman, 2000). Moreover, the peak of the spontaneous activity profile occurs at a tonotopic

locus representing a frequency that is higher than that of the inducing exposure tone (Kaltenbach and Afman, 2000). This agrees with the psychophysical finding that noise-induced tinnitus is typically matched to a frequency that is higher than that of the exposure tone (Loeb and Smith, 1967; Atherley et al., 1968).

- (5) Noise-induced hyperactivity in the DCN is correlated with tinnitus. This has been shown by behavioral studies demonstrating that animals exposed to the same intense sound conditions that cause hyperactivity in the DCN develop tinnitus-like percepts (Brozoski et al., 2002; Heffner and Harrington, 2002). Moreover, when spontaneous activity was recorded in the same animals that had previously been tested behaviorally for tinnitus, the behavioral measures of tinnitus were found to have a statistically significant correlation with the peak level of activity in the DCN (Kaltenbach et al., 2004).
- (6) The DCN possesses the type of circuit connections with the somatosensory system needed to explain some forms of somatic

tinnitus. For example, tinnitus can sometimes be modulated by stimulating the median nerve. In ~80% of tinnitus patients, the loudness or pitch of their tinnitus can be modulated by certain manipulations of the head and neck musculature (Møller et al., 1992; Levine, 1999; Møller and Rollins, 2002). This is particularly noticeable when muscles innervated by the trigeminal and upper cervical nerves, especially C2 and C3 are contracted (Levine, 1999, 2004; Levine et al., 2003; Abel and Levine, 2004). An important feature of this form of somatic tinnitus is that, when unilateral, the effective manipulation involves muscles on the side ipsilateral to the tinnitus. In addition, when accompanied by other craniofacial pathologies, the pathologies are usually on the side ipsilateral to the tinnitus (Levine, 2004). This would seem to require a circuit in which auditory inputs are integrated with ipsilateral somatosensory inputs. The DCN is one such structure, and it may be the only one where this integration is predominantly ipsilateral (Itoh et al., 1987; Weinberg and Rustioni, 1987; Wright and Ryugo, 1996; Shore et al., 2000; Shore, 2004, 2005; Zhao and Shore, 2004). Moreover, electrophysiological studies have shown that spontaneous activity of DCN neurons can be modulated by stimulation of the cervical nerves (especially C2) or certain ipsilateral cranial nerves, including the sensory branch of the trigeminal nerve (Kanold and Young, 2001) or the trigeminal ganglion (Shore, 2005).

- (7) The DCN exhibits several forms of neuronal plasticity that parallel the various forms of plasticity that characterize tinnitus. These have recently been reviewed (Kaltenbach et al., 2005). For example, both tinnitus and DCN hyperactivity often develop as a consequence of cochlear outer hair cell injury (Melamed et al., 2000; Kaltenbach et al., 2002; Rachel et al., 2002), and both persist following eighth nerve destruction (Zacharek et al., 2002). Another example of tinnitus plasticity is its common tendency to change in loudness and pitch over time (Penner,

1983, 1995; Tyler and Conrad-Arnes, 1983, 1984; Burns, 1984; Meikle, 1987; Penner and Bilger, 1992). Similarly, changes occur in the magnitude and tonotopic locus of DCN hyperactivity over time (Kaltenbach et al., 2000).

- (8) The DCN possesses circuitry and physiological properties that could explain gaze-evoked tinnitus. This form of tinnitus sometimes develops following surgeries that result in injury to the eighth nerve, and is characterized by a modulation of tinnitus that occurs when the angle of gaze is changed (Wall et al., 1987; Cacace et al., 1994a, b). A possible basis for this modulation may be the input that the DCN receives indirectly from Roller's nucleus, a vestibular-related nucleus (Kaufman et al., 2000), which is part of the brainstem perihypoglossal complex; this complex is believed to be involved in the coordination of eye movements during head displacements (McCrea et al., 1987). Neurons in Roller's nucleus project to the granule cell domain of the CN (Ryugo et al., 2003), which modulates the activity of DCN neurons. Input from this nucleus could underlie changes in the level of multiunit activity in the DCN that occur during changes in eye position during slow-wave sleep (Mori et al., 1972). Gaze-evoked tinnitus could be explained as a condition in which DCN neurons become sensitized to input from the Roller's nucleus-granule cell pathway. Such changes might be triggered by damage to the eighth nerve.

The importance of higher auditory centers in tinnitus

There is also evidence for the involvement of the IC and AC in tinnitus. Studies conducted in mice, using electrophysiological recording methods, have shown evidence for increased spontaneous activity in the central nucleus of the inferior colliculus (ICC) following intense noise exposure (Ma et al., 2006). Similar increases in spontaneous activity have been reported for this nucleus in

guinea pigs treated with sodium salicylate (Jastreboff et al., 1986; Chen and Jastreboff, 1995; Manabe et al., 1997). Studies in human subjects using fMRI have also shown that some forms of tinnitus are associated with elevated activity in the IC (Melcher et al., 2000). At the cortical level, activity increases have been demonstrated electrophysiologically in the primary AC of anesthetized cats following noise exposure (Kimura and Eggermont, 1999; Komiya and Eggermont, 2000) and in the secondary AC following treatment with salicylate or quinine (Ochi and Eggermont, 1997; Eggermont and Kenmochi, 1998). Numerous studies using positron emission tomography (PET) have shown evidence of increased activation of auditory cortical areas in human subjects with tinnitus (Arnold et al., 1996; Lockwood et al., 1998; Giraud et al., 1999; Andersson et al., 2000; Mirz et al., 2000; Wang et al., 2000; Lockwood et al., 2001). The increased activation of AC of patients with tinnitus can be modulated in the upward or downward direction by administration of lidocaine (Andersson et al., 2000; Reyes et al., 2002). In individuals whose tinnitus was made louder by lidocaine, the AC showed an increase in the level of activation in the AC, whereas those experiencing a decrease in loudness had a corresponding decrease in cortical activation (Reyes et al., 2002). However, the role of AC in tinnitus perception may be more complex than previous studies might suggest. Arnold et al. (1996) observed increased activation in the primary AC in patients who were chronically troubled by their tinnitus, but not in a chronic tinnitus patient who had no subjective complaints. They also observed increased activation of the primary AC in a chronic tinnitus patient during periods when the tinnitus was disabling, but not during periods when the patient was experiencing relief. This could mean that the AC displays increases in activity only when the tinnitus reaches some critical threshold of severity. This possibility suggests that activity in the AC might be correlated with a negative emotional response to tinnitus (see Chapter 20). Alternatively, the AC might be involved in directing attention to tinnitus, which may tend to occur when the tinnitus is more severe or troubling.

Mechanisms underlying the emergence of hyperactivity in the DCN

The changes leading to hyperactivity in the DCN may involve many different mechanisms. For example, increases in activity after noise exposure might result from shifts in the balance of excitation and inhibition at the synaptic level (Fig. 2). These shifts could arise as a direct consequence of injury or degeneration, produced either by transneuronal cell loss (Fig. 2A) or by excitotoxicity injury (Fig. 2B). In both cases, loss of normal input might trigger plastic adjustments at the synaptic level that affect the release of neurotransmitters, the number of postsynaptic receptors or even the number of synapses further downstream. Plasticity (see Chapter 3) could also lead to changes in intracellular signaling pathways that control the expression of various ion channels, thus altering the intrinsic membrane properties of neurons (Fig. 2C). This section will review literature, describing examples of each type of change, and discuss evidence for their possible involvement in the generation of neural hyperactivity and tinnitus.

Neural degeneration as a possible basis of hyperactivity

Neural degeneration in the adult central auditory system is a potentially important mechanism by which injury to the inner ear can cause hyperactivity in the DCN, since it directly affects the relative strengths of excitatory and inhibitory inputs to DCN neurons (Fig. 2). A greater loss of inhibitory synapses might cause a net disinhibition of neurons that increases their levels of spontaneous activity. The type and distribution of degenerating synapses in the CN following manipulation that are known to cause tinnitus will be discussed below.

Morest and Bohne (1983) and Kim et al. (1997) reported widespread degeneration of thick- and thin-fiber populations in all subdivisions of the chinchilla CN following octave band noise exposure. Degeneration first became apparent 4–8 days after exposure. More detailed studies of degeneration in the CN following intense noise exposure

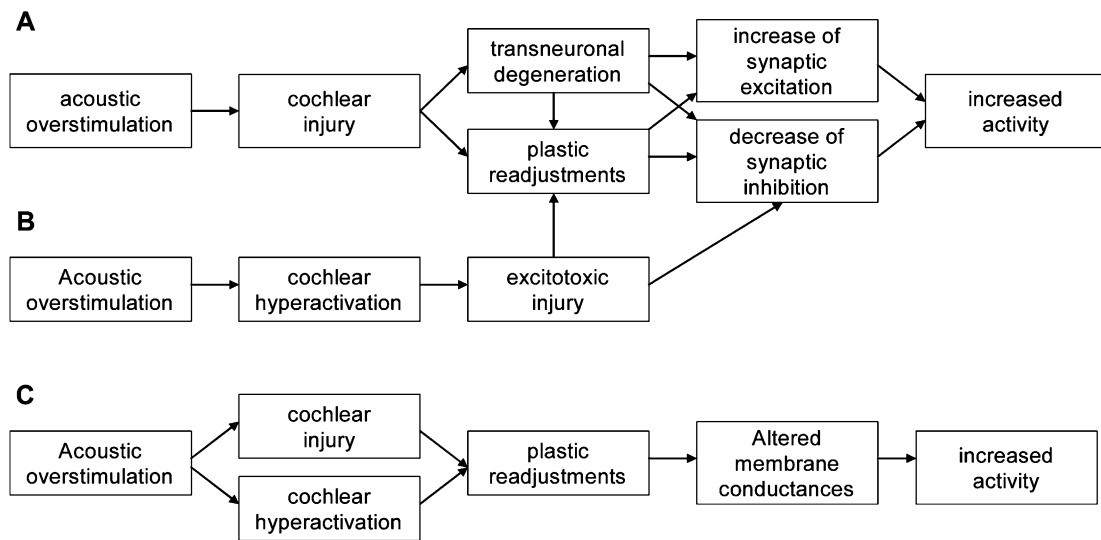


Fig. 2. Three possible mechanisms by which intense sound exposure causes an increase in spontaneous activity of DCN neurons. The first mechanism (Path A) shows increases in spontaneous activity to be the result of changes in the balance of excitatory and inhibitory inputs to DCN neurons resulting from transneuronal degeneration and plasticity triggered by cochlear injury. The second mechanism (Path B) shows a similar shift in the balance of excitatory and inhibitory inputs to DCN neurons; however, in this case the shift is due to excitotoxic injury of DCN neurons resulting from overstimulation and hyperactivity of the auditory nerve and/or excitatory neurons in the DCN. The third mechanism (Path C) shows increased activity to be the product of the intrinsic membrane properties of neurons. Such changes are brought about by altered expression of ion conductance channels that affect the cells' level of excitability. The changes in ion channel expression results from plasticity that is triggered either by hyperactivation of the auditory nerve or by loss of normal input caused by cochlear injury.

have revealed several important features. First, hair cell loss associated with degeneration of primary afferent dendrites leads to loss of fibers in the CN; in each subdivision of the cochlear nucleus, the fiber loss was found to be concentrated in one or more bands corresponding to the tonotopic loc(i)us of damaged or missing inner hair cells and/or degenerated myelinated nerve fibers observed in the cochlea (Kim et al., 1997). Some of this degeneration was limited to loss of primary afferent axons, but there was also evidence for transneuronal degeneration (see also Sie and Rubel, 1992; Zhao and Lurie, 2004). For example, after loss of eighth nerve fibers, bands of degeneration have been observed in other brainstem structures, such as the superior olivary complex (SOC) and ICC with tonotopic loci similar to those in the CN, even though no cochlear nerve fibers project further centrally than the CN (Morest et al., 1997). [Note: There is some evidence that noise exposure can also induce cell death in the DCN,

anteroventral cochlear nucleus (AVCN) and SOC by apoptosis, although the apoptotic cell types have not yet been defined (Aarnisalo et al., 2000)]. Second, degeneration sometimes appears in areas of the CN, especially the DCN, without any corresponding loss of inner hair cells or primary afferent dendrites; this degeneration was interpreted as possibly being due to excitotoxicity (Kim et al., 1997). Third, the degeneration process can continue for many months. The numbers of degenerated fibers and degenerated pre-synaptic terminals are not constant but vary considerably over time; these degenerative changes are accompanied by sprouting of axons and formation of new synapses (Benson et al., 1997; Bilak et al., 1997; Kim et al., 2004a, b). Thus, noise-induced injury is a chronic, ongoing problem that continues long after termination of the exposure and beyond the period of primary afferent degeneration. Fourth, the degeneration and re-growth processes result in a greater loss of inhibitory than

excitatory synapses (Kim et al., 2004b). This is because excitatory synapses in the ventral cochlear nucleus (VCN) make a more complete recovery than inhibitory synapses. This recovery may thus favor an increase in excitation. An increase in excitation is consistent with the losses of glycinergic neurotransmission in the VCN following cochlear ablation (Suneja et al., 1998a, see below). A similar relationship may exist in the DCN where noise exposure causes increases in spontaneous activity and decreases in glycinergic input (Asako et al., 2005).

Changes in cell size as a possible basis of hyperactivity

Cell shrinkage is another variant form of degeneration. Reductions in the size of cochlear nucleus cells have been observed following various kinds of manipulations that affect primary afferent input to the CN, such as blockage of outer or middle ear conduction (Webster and Webster, 1979), pharmacological block of primary afferent activity (Pasic and Rubel, 1989), induction of ototoxic injury (Lustig et al., 1994; Lesperance et al., 1995; Kawano et al., 1997) and anatomical deafferentation by cochlear ablation (Asako et al., 2005). Reductions of cell size have also been observed in brainstem auditory nuclei of humans following adult-onset deafness (Moore et al., 1997). In animals, the reduced cell volumes following the various manipulations of peripheral input have been observed mainly in the AVCN, although one recent study reported a decrease in the soma area of DCN tuberculoventral cells 2 weeks following cochlear ablation (Asako et al., 2005). The cell volumes of fusiform cells in the DCN appear unaffected by these manipulations (Asako et al., 2005), probably reflecting the relatively stronger share of supportive input from descending and intrinsic pathways (Kane and Finn, 1977; Kane and Conlee, 1979).

Reductions in cell size could lead to changes in the shape of action potentials, possibly decreasing their durations. There is evidence that neurons with shorter duration spikes have weaker synaptic strength, and thus weaker neurotransmitter release

than larger neurons (Sabatini and Regehr, 1997); postsynaptic neurons might therefore be expected to have decreased firing rates. Thus, even if most DCN cells do not themselves change in volume, their activity could be affected by reductions in cell volumes of AVCN neurons, since some neurons from the AVCN project directly to DCN neurons. Ventrotubercular neurons are located in the AVCN and posteroventral cochlear nucleus (PVCN) and project to the DCN where they influence the levels of neuronal activity. For example, Evans and Nelson (1973) observed inhibition of DCN neurons in response to electrical stimulation of the AVCN. Zhang and Oertel (1993) distinguished two types of stellate cells in the VCN, having opposite effects on DCN neurons. They found that D-stellate cells have an inhibitory effect on DCN tuberculoventral cells whereas T-stellate cells have an excitatory effect. Tuberculoventral cells, also known as vertical or corn cells, inhibit DCN principal neurons (Voigt and Young, 1980; Young and Voigt, 1982; Zhang and Oertel, 1993). If the cells that are excitatory to DCN neurons shrink after loss of primary afferent input, the effect might be a decrease in spike duration and weaker synaptic strength producing a decrease in their excitatory effects on DCN neurons. Shrinkage may also decrease the metabolic capacity of neurons to process neurotransmitters for release. If shrinkage involves VCN cells that normally have an inhibitory influence on DCN neurons, the effect might be a reduction in the strength of inhibition of DCN neurons. This could lead to a disinhibition of some DCN cells with a resulting increase in their spontaneous activity.

The role of neural plasticity as a basis of hyperactivity

The importance of neural plasticity in the etiology of tinnitus has been discussed in several recent reviews (Syka, 2002; Eggermont and Roberts, 2004; Kaltenbach et al., 2005; Møller, 2006) (see Chapter 3). Plastic alterations have been identified in the DCN following exposure to several types of tinnitus-inducing agents, including intense sound, aminoglycosides, cisplatin and sodium salicylate.

Most of the changes reported have been observed at the synaptic level, although this may be due partly to the fact that synapses have been the focus of these studies. Plastic changes also occur at other cellular levels, such as the intracellular environment and cell membranes. Below is a summary of the relevant research findings.

Changes in neurotransmitter release/uptake

Tinnitus often develops after injury or destruction of the eighth nerve, and there is evidence that this type of trauma can trigger changes in the balance of inhibitory and excitatory neurotransmission in all subdivisions of the CN. In the DCN, the release of the inhibitory transmitter, glycine, was reduced by ~40% and its uptake was increased by ~50%, 59 days after cochlear ablation (Suneja et al., 1998a; Potashner et al., 2000). The decrease continued until at least 145 days of survival when the glycine release dropped to 50% of the pre-ablation level. In the DCN decreases in the number of glycine-immunoreactive puncta, presumably representing presynaptic terminals, were observed on the somata of fusiform cells 14 days following bilateral cochlear ablation (Asako et al., 2005); decreases were also observed on the somata of spherical, globular bushy, stellate multipolar and radiate cells of the VCN. Some of these changes would presumably weaken inhibitory effects on fusiform cells, thus potentially raising their levels of spontaneous activity.

On the other hand, increases in spontaneous activity could also result from increased release of excitatory transmitters. Transmitters that are excitatory to DCN neurons include glutamate or aspartate, acetylcholine and possibly serotonin. Large declines in the release of the excitatory transmitters, glutamate and D-aspartate occur in the CN after cochlear ablation (Potashner et al., 1997; Wenthold and Gulley, 1977). In the DCN the release of D-aspartate, showed a 50% decline from 2 to 145 days following ablation of the ipsilateral cochlea (Potashner et al., 1997). The decreases in D-aspartate release were even larger in the VCN, although these tended to recover to control levels by 59 days post-ablation (Potashner

et al., 1997). Thus, no evidence of a net increase in glutamate release was observed in any subdivision of the CN following cochlear ablation. However, increases in the release of aspartate have been observed in chinchillas exposed to intense noise (Muly et al., 2004). The ventral part of the DCN showed a nearly three-fold increase in evoked aspartate release, 7 days after noise exposure; this was followed by a nearly complete decline at 14 days post-exposure, then by a large increase in release to more than twofold above the control level 90 days after exposure. The dorsal part of the DCN showed only decreases in aspartate release following noise exposure. Noise exposure thus seems to have different effects on neurotransmission from those caused by ablation. This is consistent with the recent finding that DCN hyperactivity caused by intense sound exposure is different from that caused by outer hair cell loss, even when the volume and spread of hair cell loss is about the same (Carron et al., 2006).

Although no direct measures of acetylcholine release following deafferentation have been reported, there is evidence for an increase in choline acetyl transferase (ChAT), the enzyme of acetylcholine synthesis, after intense sound exposure (Jin et al., 2006). Such increases were observed mostly in the granule cell region and are suggestive of an increase in cholinergic transmission to granule cells.

Plastic alterations have also been observed in serotonin activity in the DCN following noise exposure (Cransac et al., 1998). This transmitter is released by non-auditory inputs to the CN from the dorsal raphe nucleus (Klepper and Herbert, 1991; Thompson et al., 1995; Thompson and Thompson, 2001). Both excitatory and inhibitory effects of serotonin on CN neurons have been reported, although mainly neurons in the VCN have been studied and these effects were found to be mostly inhibitory. There is a relatively greater share of serotonergic input to the DCN, although its influence on DCN neurons has yet to be established. Upregulation of serotonin activity in the DCN were found to increase with the level of noise exposure (Cransac et al., 1998). This upregulation might contribute to the emergence of hyperactivity.

Changes at the receptor level

There are numerous indications that receptors for excitatory and inhibitory transmitters may be altered by manipulations similar to those that cause changes in neurotransmitter release. Suneja et al. (1998b) found evidence for changes in glycine receptor expression in all three subdivisions of the CN after unilateral cochlear ablation. In the deep layer of the DCN, binding of ^3H -strychnine, an antagonist of the glycine receptor, was unchanged at 2–7 days post-ablation, slightly increased at 31 days and decreased by ~25% at 60 days post-ablation. In the fusiform cell layer, ^3H -strychnine binding displayed a downward trend up to 2 months after ablation.

Changes in binding to AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors for glutamate or aspartate following cochlear ablation have also been studied in auditory brainstem nuclei, including each of the three layers of the DCN (Suneja et al., 2000). The molecular and fusiform cell layers of the ipsilateral DCN showed only marginal increases in AMPA binding 2 days after ablation. However, increases in AMPA binding were significant in the deep layer of the DCN 7 days after ablation, but at 60 days, binding in the deep layer was slightly decreased. Cochlear ablation can also trigger rearrangement in the distribution of AMPA receptors on DCN fusiform cells (Rubio, 2006). These changes are indicative of alterations in the number and function of glutamate receptors and could contribute to the changes in the level of spontaneous activity of postsynaptic neurons following cochlear insult.

Various lines of evidence point to changes in receptors for the excitatory transmitter, acetylcholine, following loss of normal cochlear input. There are both nicotinic and muscarinic receptors for acetylcholine in the CN (Chen et al., 1994; Morley and Happe, 2000), although much larger changes in DCN spontaneous activity are induced by muscarinic than by nicotinic agents (Chen et al., 1994). Previous noise-exposure causes enhancements in the responses of DCN neurons to the cholinergic agonist, carbachol. Such enhancements have been observed in the superficial DCN (molecular and fusiform cell layers)

both in vitro (Chang et al., 2002) and in vivo (Kaltenbach and Zhang, 2006). Neurons with the properties of cartwheel cells (bursting activity) showed enhanced excitatory responses to carbachol 7–39 days following noise exposure, whereas multiunit ensembles recorded from the fusiform cell layer showed enhanced inhibitory responses. The enhanced excitation of putative cartwheel cells may result from an upregulation of acetylcholine receptors in the granule cell regions. Granule cells provide the main excitatory input to cartwheel cells, and recent evidence indicates that loss of cochlear input to the CN can cause an increase in the number of acetylcholine receptors in the granule cell regions of the CN and in the fusiform cell layer (Jin and Godfrey, 2006), which also includes granule cells. Although the identities of all the cell types that become hyperactive are not yet known, the available evidence suggests that both cartwheel cells and fusiform cells are likely sources (Brozoski et al., 2002; Chang et al., 2002; Kaltenbach and Zhang, 2006). Which cell type contributes more to the condition of hyperactivity may be dependent on the state of activation of granule cells, which likely depends on the number of acetylcholine receptors and the volume of cholinergic inputs to the granule cell domain.

Changes in the number of synapses

Changes in transmitter release and uptake as well as in the number of receptors, as just described, may ultimately reflect changes in the number of active synapses. Several recent papers report that loss of cochlear input, due either to cochlear ablation or noise-induced hearing loss, leads to an increase in the number of cholinergic synapses in the CN (Meidinger et al., 2006). Thus staining for GAP-43, a marker for synaptic remodeling, was found to increase in much of the VCN following cochlear ablation (Illing et al., 1997, 2005) and noise exposure (Michler and Illing, 2002; Illing et al., 2005; Meidinger et al., 2006). No mention was made of such changes in the DCN or in the granule cell regions. However, Jin et al. (2006) reported increases in the expression of ChAT following intense tone exposure in the granule cell

regions of the hamster DCN. This enzyme is present in the presynaptic terminals of cholinergic neurons where it is involved in the synthesis of acetylcholine. Jin et al. (2006) interpreted the increase in ChAT expression as indicative of a possible increase in the number of cholinergic terminals in the granule cell regions.

Sprouting of new synapses in the DCN and VCN following cochlear ablation has been reported, although the available evidence indicates that the degree in the adult DCN is probably much less than in the VCN (Benson et al., 1997). In the DCN of guinea pigs an increase in the number of synapses was observed in the deep layer 4 days after unilateral cochlear ablation, despite loss of primary afferents at this time; no changes in the number of synapses was apparent in the DCN from 7 days through 161 days postablation. In contrast, evidence for synaptogenesis in the AVCN of the same animals was more apparent after 7 days postablation, and followed a period of degeneration of primary afferents at 4 and 7 days (Benson et al., 1997).

Evidence for synaptic sprouting in the VCN of chinchillas after acoustic overstimulation has been reported in several studies (Bilak et al., 1997; Muly et al., 2002; Kim et al., 2004a, b). Kim et al. (2004a, b) examined patterns of synaptic change in the AVCN and PVCN over a period of 6–8 months following a single 3-h exposure to octave band noise (centered at 4 kHz) at a level of 108 dB SPL. In the AVCN, degeneration of excitatory and inhibitory synaptic terminals was observed around the somata and dendrites of globular bushy cells as well as in the neuropil. This degeneration was followed and accompanied by the emergence of new synapses distinguished by their small size and lower number of vesicles. The new synapses appeared to fill in the vacated spaces left by loss of the original terminals. Both degeneration and synaptogenesis were observed chronically and found to continue for the entire 8 months of observation. Degeneration of excitatory and inhibitory synapses was also seen in the PVCN. The recovery of synapses around the somata of PVCN neurons and in the neuropil was less complete for the inhibitory than for the excitatory terminals. This led to a net decrease in the inhibitory input to

these elements. This would seem to favor an increase in neuronal excitation. Whether a similar net loss of inhibitory synapses occurs in the DCN has not yet been established, although the loss of glycine receptors in the DCN following cochlear ablation, as described above, would be consistent with a decrease in inhibitory synapses. DCN hyperactivity could result from a loss of glycine receptors and/or glycinergic synapses from the DCN, from a loss of inhibitory synapses of VCN neurons that project to DCN neurons or from an increase in excitatory input from the VCN. It is also possible that DCN hyperactivity may be associated with hyperactivity in the VCN. However, no studies have yet reported increases in spontaneous activity in the VCN after intense noise exposure or cochlear insult. Future studies are needed to shed more light on these possibilities.

Changes in ion conductance

Changes in ion conductances are not necessarily independent of the changes discussed above. Indeed, changes in ion channels are to be expected if there are changes in synaptic receptors since many receptors are ionotropic and therefore include ion channels as part of their tertiary structures. Other receptors indirectly control ion channels that are distributed elsewhere, either by their influence on intracellular signaling pathways or by their effects on membrane voltages. Changes in ion conductance are of special interest and are considered here because of their role in controlling ion permeability of the cell membrane. This function determines the resting membrane potential, the threshold of spike generation, the duration of action potentials and the time course of recovery from action potentials. They can thus be considered pivotal in determining the excitability of neurons and, therefore, their spontaneous discharge rates. Despite their importance, relatively little is known about the effects of tinnitus-inducing manipulations on ion channels of DCN neurons. Several published studies have focused on the VCN, which is relevant to activity in the DCN, as it receives direct input from the VCN.

Francis and Manis (2000) examined the effects of bilateral cochlear ablation on the membrane properties of neurons in the AVCN. The cochleae were removed in 1-month-old rats, and the animals were studied electrophysiologically in brain slices 2 weeks later. Deafferented AVCN neurons showed more depolarization and smaller action potentials, smaller afterhyperpolarizations and shorter membrane time constants compared to those in control animals. Other neurons showed evidence for increases in input resistance. The authors' explanation for these changes was that they might reflect alterations in cell size or changes in the composition, properties or spatial distribution of voltage-dependent ion channels. However, only a few published studies have examined changes in ion channels in the VCN after cochlear ablation. Caminos et al. (2005) found no changes in the expressions or spatial distributions of Kv1.1 or Kv1.2 potassium channels in AVCN neurons 10 days after bilateral cochlear ablation in young adult rats. Leao et al. (2005) found no difference in Ih channels or membrane excitability when spherical bushy cells in the AVCN of normal hearing CBA mice were compared with those of congenitally deaf mice. A more recent study reported changes in the expression of the two-pore domain potassium channel in the rat cochlear nucleus following bilateral cochlear ablation (Holt et al., 2006). It is not yet clear in which subdivision these changes occur, but the results revealed a sustained decrease in transcripts over three recovery times for three subunits (TASK-1, 2 and 5). Transcripts for three other subunits (TWIK-2, TREK-1 and TREK-2) were expressed at normal levels 3 days after ablation but decreased at 3 weeks and 3 months. Two subunits (TRAAK and TASK-3) were decreased at 3 days, but returned to their normal levels of expression at the 3-week and 3-month time frames. The lattermost changes thus suggest plastic changes of the two-pore domain potassium channel in response to deafferentation. Such changes could be important factors controlling both spontaneous activity and responses to sound, since one function of the two-pore domain potassium channel is to set the resting membrane potential.

Changes in cell signaling proteins

Ultimately, disturbances in transmitter release, receptors binding, numbers of synapses and numbers of ion channels may reflect alterations in regulatory pathways and intracellular signaling cascades. Changes in neurotransmission caused by cochlear ablation are accompanied by alterations in the expression of numerous enzymes of signal transduction pathways, such as cyclic-AMP dependent protein kinase (PKA), protein kinase C (PKC), calcium/calmodulin-dependent protein kinase (CaMKII), (Garcia et al., 2000; Zhang et al., 2003, 2004; Yan et al., 2006), phosphorylated cAMP response element-binding protein (CREB) (Illing and Michler, 2001; Michler and Illing, 2003; Mo et al., 2006), extracellular signal-regulated kinase (ERK) and stress-activated protein kinase (SAPK) (Suneja and Potashner, 2003). Some of these play roles in regulating transmitter release or receptor binding (Yan et al., 2006). Changes in the numbers of synapses following deafferentation are also accompanied by increases in growth factors in the cochlear nucleus. Examples include increases in neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF) after cochlear ablation (Suneja et al., 2005), and increases in fibroblast growth factors after acoustic injury (Smith et al., 2002). These changes are triggered by the loss of synapses and provide stimulation for the growth of new synapses.

Net effects of altered input to the cochlear nucleus (Fig. 3)

Decreases in inhibition

To summarize, several lines of evidence indicate that manipulations that result in loss of normal input (both anatomical and functional) to the auditory brainstem cause a decrease in inhibition in the DCN that is greater than the decreases in excitation (Fig. 3). Such decreases are observed in the DCN as declines in glycine release (Suneja et al., 1998a; Potashner et al., 2000) and reductions of glycine immunoreactivity after cochlear ablation (Asako et al., 2005), and greater reductions in

Synaptic mechanisms underlying DCN hyperactivity

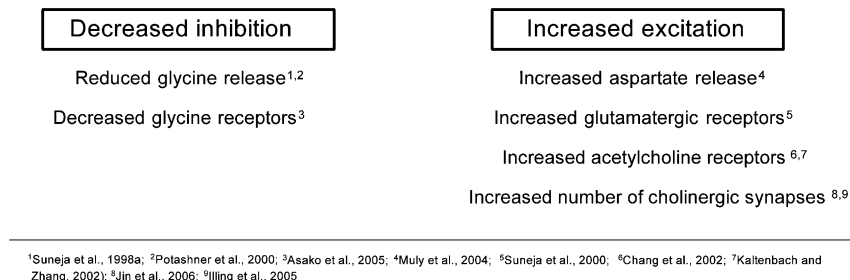


Fig. 3. Summary of changes likely to contribute to the generation of hyperactivity in the DCN. The changes shown here have been shown to occur in the DCN as a consequence of noise exposure, cochlear ablation and/or other manipulations that are tinnitus inducing.

the number of inhibitory synapses than excitatory synapses after either cochlear ablation or noise exposure (Kim et al., 1997; Morest et al., 1998; Muly et al., 2002). Such changes likely involve plastic readjustments to loss of input since they continue to occur long after the period when loss of primary afferent fibers is observed. Increased spontaneous activity in the DCN might be a direct consequence of this loss of glycinergic function. This seems likely given that blockade of glycine receptors in animals with intact primary afferent input to the DCN can produce increases in spontaneous activity of DCN principal neurons and cartwheel cells (Caspary et al., 1987; Evans and Zhao, 1993; Zhang and Oertel, 1994; Davis and Young, 2000). These considerations suggest that loss of inhibitory influence on DCN neurons, particularly on the fusiform cells, may be the dominant mechanism underlying the emergence of hyperactivity in the DCN after peripheral insult.

Increased excitation

As just explained, increases in excitation might be expected based on the observations that loss of inhibition is greater than the loss of excitation. However, further increases in excitation seem likely because loss of inhibition is associated with increases in the number of excitatory synapses. Evidence for increased excitation in the DCN, after loss of normal anatomical or functional input

from the cochlea, includes increases in AMPA binding after cochlear ablation and increases in glutamatergic transmitter release following noise exposure (Muly et al., 2004). The increases in transmitter release were apparent in the ventral part of the DCN 7 and 90 days after the initial insult, but were reduced at 14 days. These changes in glutamatergic transmission reflect synaptic plasticity and cannot explain the persistence of hyperactivity at 14 days (Kaltenbach et al., 2000). However, excess glutamate release could cause further injury to DCN neurons through the mechanism of excitotoxicity (Fig. 2B), which could, in turn, result in damage to inhibitory interneurons, such as cartwheel and stellate cells. Permanent loss or damage to these cells could cause chronic disinhibition of fusiform cells, leading to chronic increases of fusiform cell activity. The increase in glutamatergic neurotransmission thus seems likely to be an important mechanism contributing to the generation of tinnitus-related hyperactivity in the DCN. Chronic hyperactivity also has a cholinergic component, which probably acts on the DCN through granule cells. There is evidence for increased binding to cholinergic receptors after cochlear ablation (Jin and Godfrey, 2006) and increased sensitivity of the DCN to cholinergic agonists after noise exposure (Chang et al. 2002; Kaltenbach and Zhang, 2006). These increases would tend to raise the firing rates of cartwheel and stellate cells, the targets of granule cells, thus enhancing their contribution to hyperactivity.

Increased membrane excitability

Evidence has been presented for changes in the expression of ion conductance channels that influence cellular excitability levels independent of neurotransmitter receptors. Chief among these is the two-pore domain potassium channel. Expression of this channel has been shown to decrease in the CN following cochlear ablation. It is not yet clear in which subdivision this decrease occurs or whether this change also occurs following other tinnitus-inducing manipulations. However, changes in the two-pore domain potassium channel may be an important factor contributing to hyperactivity, in view of its role in controlling a cell's excitability and in altering the resting membrane potential (Millar et al., 2000).

Summary and conclusions

The evidence presented above supports a role of the DCN in the generation and modulation of tinnitus. There is growing support for the hypothesis that at least some forms of tinnitus are linked to increased spontaneous activity in the DCN. Animal studies have shown that loss or reduction of normal peripheral input, such as occurs following intense noise exposure, cochlear ablation and ototoxic injury, causes both decreases in inhibitory (glycinergic) and increases in excitatory (glutamatergic and cholinergic) neurotransmission in the DCN. These changes arise as a consequence of degeneration of synapses, expression of synaptic plasticity and probably also because of injuries caused by excitotoxicity. Changes in the ion conductance properties of neurons, outside synapses, may also contribute to the observed changes in spontaneous activity, although this possibility is only now beginning to be explored. It seems reasonable to expect that knowledge about changes in cellular processes that may be involved in causing the abnormal neural activity that results in tinnitus will stimulate new approaches for the treatment of tinnitus.

Acknowledgments

This work was supported by funds from NIDCD R01 DC003258. I would also like to thank my

colleagues, Drs. Aage Møller and Paul Finlayson as well as Frank Licari for their valuable comments on the manuscript.

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CHAPTER 10

Neural mechanisms underlying somatic tinnitus

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Abstract: Somatic tinnitus is clinically observed modulation of the pitch and loudness of tinnitus by somatic stimulation. This phenomenon and the association of tinnitus with somatic neural disorders indicate that neural connections between the somatosensory and auditory systems may play a role in tinnitus. Anatomical and physiological evidence supports these observations. The trigeminal and dorsal root ganglia relay afferent somatosensory information from the periphery to secondary sensory neurons in the brainstem, specifically, the spinal trigeminal nucleus and dorsal column nuclei, respectively. Each of these structures has been shown to send excitatory projections to the cochlear nucleus. Mossy fibers from the spinal trigeminal and dorsal column nuclei terminate in the granule cell domain while *en passant boutons* from the ganglia terminate in the granule cell domain and core region of the cochlear nucleus. Sources of these somatosensory–auditory projections are associated with proprioceptive and cutaneous, but not nociceptive, sensation. Single unit and evoked potential recordings in the dorsal cochlear nucleus indicate that these pathways are physiologically active. Stimulation of the dorsal column and the cervical dorsal root ganglia elicits short- and long-latency inhibition separated by a transient excitatory peak in DCN single units. Similarly, activation of the trigeminal ganglion elicits excitation in some DCN units and inhibition in others. Bimodal integration in the DCN is demonstrated by comparing responses to somatosensory and auditory stimulation alone with responses to paired somatosensory and auditory stimulation. The modulation of firing rate and synchrony in DCN neurons by somatosensory input is physiological correlate of somatic tinnitus.

Keywords: somatic tinnitus; somatosensory; trigeminal; nonauditory pathways; cochlear nucleus

Introduction: somatic tinnitus

There has long been evidence that connections exist between higher-order neurons subserving different senses (e.g., some neurons serve both the auditory and entorhinal cortices). But only in

recent years has it become apparent that these connections exist even in first and second order neurons of the brainstem — and, further, that the connections are functional even in normal animals. How might these connections manifest clinically?

Approximately two-thirds of individuals with tinnitus can modulate the loudness or pitch of their tinnitus by voluntary or external manipulations of the jaw, movements of the eyes, or

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pressure applied to head and neck regions, including the temporomandibular joint (Rubinstein et al., 1990; Pinchoff et al., 1998). In some cases, the necessary manipulations reported were forceful (e.g., Abel and Levine, 2004), while in others less vigorous manipulations could produce the changes in perceived loudness and or pitch of the tinnitus (Pinchoff et al., 1998). In addition, there is an increased prevalence of somatoform disorders in individuals with tinnitus (Hiller et al., 1997), as well as reports of tinnitus occurring after dental pulp-algia that resolved after endodontic therapy (Wright and Gullickson, 1996). Tinnitus is also associated with upper craniocervical imbalances such as prolapsed intervertebral disks or instability of the craniocervical junction, which can be resolved following stabilization surgery (Montazem, 2000). Similarly, tinnitus occurs more frequently in patients who have craniocervical mandibular disorders such as temporomandibular joint syndrome (Chole and Parker, 1992; Morgan, 1992; Gelb et al., 1997).

These factors have something in common: they all involve stimulation of the somatosensory system, usually associated with the jaw, temporomandibular joint, extra-ocular muscles, and the neck. While most reported changes in tinnitus involve somatosensory regions of the head and neck, changes in tinnitus can even occur with stimulation of the median nerve or upper limbs (Møller et al., 1992; Cacace et al., 1999), all leading to the term “somatic tinnitus.”

These observations imply that there are neural connections between somatosensory centers and auditory centers, at least in individuals with somatic tinnitus. Do these connections also exist in the normal system? How would they function to modulate an existing tinnitus? Could they play a role in generating tinnitus?

This chapter will describe the functional anatomy of these sensory interactions and will demonstrate physiological properties that could account for somatic tinnitus, i.e., the *modulation* of an existing tinnitus. Some attention will be given to the idea that the *generation* of tinnitus may be influenced by a functional reorganization of auditory–somatosensory interactions after diminished afferent inputs to either auditory or

somatosensory centers, e.g., following noise-induced hearing loss or tooth abscess.

Anatomical substrates of somatic tinnitus

Overview of the somatosensory system

Perception of touch, temperature and pain are all associated with the somatosensory system as is proprioception. They involve neural processes that result in a conscious awareness of a physical stimulus that begin at the periphery of the somatosensory system. Here, specialized sensory receptors transform mechanical stimuli into electrical discharges in the nerve fibers innervating the sensory organ to convey somatic sensory information from various parts of body. Somatic sensation from the trunk, limbs, and neck are mediated by afferent fibers the cell bodies of which are located in the dorsal root ganglia (DRG). Sensation from the head, neck, and face is conveyed by the trigeminal nerve, the cell bodies of which are located in the trigeminal ganglion (TG). The encoded somatic information is then conveyed into the brain via distinct pathways.

Central processes of the DRG ascend in the brain primarily via two pathways: the spinothalamic pathway of the anterolateral system and the dorsal column-medial lemniscal system. Each pathway conveys different sensory modalities. The anterolateral system mediates pain, temperature, and some deep touch, in which nociceptive neurons are mainly located in the superficial layer (lamina I) and the substantia gelatinosa (lamina II) of the dorsal horn. The dorsal column-medial lemniscal system primarily mediates proprioception and discriminative sensation, and consists of two nuclei: nucleus cuneatus, which serves the upper trunk and limbs, and nucleus gracilis, which serves the lower trunk and limbs.

Central processes of the TG terminate in the brainstem trigeminal sensory complex, which comprises three groups of nuclei that mediate different sensory modalities: The principle nucleus receives information about discriminative sensation and light touch; the mesencephalic nucleus receives proprioceptive information from the jaw; and the

spinal trigeminal nucleus (Sp5) receives information about pain and temperature as well as gentle pressure and vibrissa deflection (Hayashi et al., 1984; Jacquin et al., 1989). Sp5 also receives proprioceptive inputs from vocal tract/intra oral structures such as the temporomandibular joint and tongue muscles (Romfh et al., 1979; Jacquin et al., 1989; Nazruddin et al., 1989; Takemura et al., 1991; Suemune et al., 1992). The Sp5 can be divided into three groups of nuclei: pars oralis (Sp5O), pars interpolaris (Sp5I), and pars caudalis (Sp5C). The Sp5C contains three layers: (1) the subnucleus magnocellularis; (2) the subnucleus gelatinosus; and (3) the outmost subnucleus marginalis (Darian-Smith et al., 1963; Usunoff et al., 1997). The subnucleus gelatinosus, which is analogous to the lamina II in the spinal cord, primarily receives nociceptive afferents.

Both primary and secondary somatic sensory neurons project to the auditory system. The following section will review the anatomy of these pathways with emphasis on the somatosensory projections to the cochlear nucleus (CN).

Projections from primary somatic sensory neurons to the CN

DRG axons and fibers of the trigeminal nerve project to the ventral CN (VCN) (Pfaller and Arvidsson, 1988; Zhan et al., 2006). The projection cells generally are small in size ranging from 15 to 20 μm in diameter in the DRG (Zhan et al., 2006), and 10 to 45 μm in the TG (Shore et al., 2000). These small projection cells may belong to the category of type B cells, which usually give rise to unmyelinated or lightly myelinated fibers (Zhan et al., 2006).

The CN projection cells in the TG are located in the medial portion (the ophthalmic division) and lateral portion of the ganglion (the mandibular division) (Shore et al., 2000). The terminal field of the TG-to-CN projection is primarily located in the shell regions of the CN but there are also terminals in some magnocellular regions of ventral CN (VCN). The TG-to-CN projection fibers are thin (approximately 1 μm) and typically form *en passant boutons*, mostly clustering around the

medial and lateral edges of VCN. Postsynaptic targets of TG terminals in the VCN include dendrites of granule cells and large cells, and lumina of blood vessels (Shore et al., 2000).

The CN projection cells in the DRG are located at the C2 level. The terminal fields of these projection cells are concentrated along the medial edge of the VCN, dorsal ridge of the AVCN (i.e., subpeduncular corner between the AVCN and the inferior cerebellar peduncle), and lamina of the granule cell domain (GCD) (Pfaller and Arvidsson, 1988; Zhan et al., 2006). The GCD includes the shell region and the fusiform cell layer of the dorsal CN (DCN) that both contain numerous small cells (Weedman and Ryugo, 1996; Zhou and Shore, 2004). Terminal endings of the C2 DRG-to-CN projection fibers have varied size and shapes, and are not readily identified as boutons or mossy fibers (Zhan et al., 2006). Postsynaptic targets of the C2 DRG projection include the primary dendrites of unipolar brush cells, and the distal dendrites of granule cells.

Projections from secondary somatic sensory neurons to the CN

Secondary somatic sensory neurons that project to the CN are located in the Sp5 (Zhou and Shore, 2004; Haenggeli et al., 2005) and dorsal column nuclei (Itoh et al., 1987; Weinberg and Rustioni, 1987; Wright and Ryugo, 1996; Wolff and Kunzle, 1997; Zhou and Shore, 2004).

The Sp5I and the Sp5C contain the majority of projection cells from Sp5 to the CN. In Sp5I, projection cells are located in the dorsomedial and marginal areas (Fig. 1); in Sp5C, projection cells are located in either the subnucleus marginalis or the subnucleus magnocellularis. The subnucleus gelatinosus of Sp5, however, contains very few projection cells (Fig. 1D), suggesting that the nociceptive Sp5 neurons may not directly project to the CN (Zhou and Shore, 2004). The CN projection cells in the Sp5 have varied morphologies: either polygonal somata (ranging from $10 \times 12 \mu\text{m}$ to $25 \times 28 \mu\text{m}$ in diameter), or elongated somata (10×30 – $7 \times 40 \mu\text{m}$) (Fig. 1), (Wolff and Kunzle, 1997; Zhou and Shore, 2004; Haenggeli et al.,

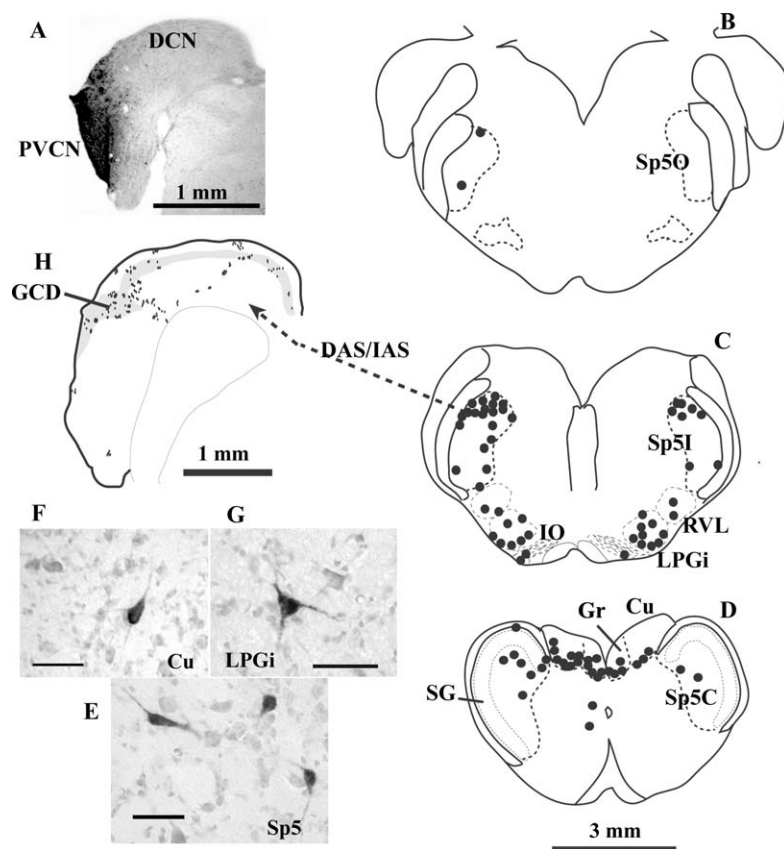


Fig. 1. Projections from Sp5 to the CN in the guinea pig. (A–G) Retrograde labeling in the brainstem after an injection of biotinylated dextran amine (BDA) into the CN. (A) Photomicrograph of the injection site. The injection site is virtually restricted to the shell region of the PVCN. (B–D): Drawings of 1 mm transverse sections across the medulla. Each dot represents one labeled cell. The labeled neurons are located primarily on the ipsilateral side of Sp5, in the Sp5I and Sp5C. Very few labeled cells, if any, are located in the SG (D). Labeled neurons can also be found in the medular reticular formation (RVL and LPGi, C), inferior olive (IO, C), and dorsal column nuclei (Gr and Cu, D). Projection neurons in Sp5 have either polygonal or elongated somata (E). Projection neurons in dorsal column nuclei and reticular formation are multipolar (F and G). (H) Terminal labeling in the CN after placement of an anterograde tracer into Sp5I. Most Sp5 fibers enter the CN via DAS/IAS and terminate primarily in the GCD (gray area), but also in deep DCN. Each dot represents one to three labeled terminal endings. Scale bars = 25 µm (E–G). (Abbreviations: CN, cochlear nucleus; Cu, cuneate nucleus; DAS, dorsal acoustic striae; DCN, dorsal cochlear nucleus; GCD, granule cell domain; Gr, gracile nucleus; IAS, intermediate acoustic striae; IO, inferior olive; LPGi, lateral paragigantocellular reticular nucleus; PVCN, posteroventral cochlear nucleus; RVL, rostral ventrolateral reticular formation; SG, subnucleus gelatinosus; Sp5, spinal trigeminal nucleus; Sp5C, pars caudalis of Sp5; Sp5I, pars interpolaris of Sp5; Sp5O, pars oralis of Sp5).

2005). Their projection fibers and terminal endings are either small to medium *en passant boutons*, or large, irregular terminal swellings that resemble mossy fibers. The small Sp5 terminal endings are scattered across the entire CN, making synaptic contacts with granule cells or large principal cells (Zhou and Shore, 2004). The Sp5 mossy fibers are primarily located in the GCD, making synaptic

contacts with granule cells (Zhou and Shore, 2004; Haenggeli et al., 2005).

The CN projection neurons in the dorsal column nuclei usually have polygonal somata, and aggregate in the ventral edge of the dorsal column nuclei (Fig. 1D). Like the Sp5 projections, the fibers of CN projection neurons from the dorsal column nuclei primarily terminate in the

GCD, in the forms of mossy fibers and boutons (Itoh et al., 1987; Weinberg and Rustioni, 1987; Wright and Ryugo, 1996; Wolff and Kunzle, 1997). The postsynaptic targets of these mossy fibers include dendrites of granule cells (Wright and Ryugo, 1996). Secondary neurons in another ascending pathway of the DRG, the anterolateral system that mediates pain and temperature, have not been reported to project to the auditory structures. This again suggests a lack of direct nociceptive projections from the somatosensory system to the auditory system.

Mossy fibers are the predominant terminal endings of projection fibers from the secondary sensory nuclei (i.e., Sp5 and dorsal column nuclei) to the CN, whereas projections from the primary somatic ganglion cells (TG and DRG) terminate in the CN as small, en passant endings. It is currently unknown whether or not these morphological differences in termination may translate into distinct alterations of CN activity. The small terminals of TG projection fibers tend to make contacts with a variety of cells, including principal cells in VCN, and thus may *directly* affect CN output activity. Mossy fibers are located mostly in the GCD and make contacts with granule cells, whose axons, the parallel fibers, synapse on the apical dendrites of the fusiform cells — the principal output neurons of the DCN. Therefore, the secondary somatic sensory neurons *indirectly* affect DCN output via the mossy fiber-parallel fiber-fusiform cell pathway (as well as via inhibitory interneurons) (see physiology section “Effects of dorsal root ganglion and dorsal column activation on DCN activity”).

Projections from the somatosensory system to the inferior colliculus

In addition to their projections to the CN, somatic sensory neurons project to other central auditory structures, including inferior colliculus (IC). The IC projection cells are mainly found in the dorsal column nuclei and Sp5 (Zhou and Shore, 2006). Some neurons in the Sp5 and the dorsal column nuclei project to both the CN and the external cortex of IC by way of axon collaterals (Li and

Mizuno, 1997). IC projection cells have not been reported in the TG. Projection fibers from these somatic sensory neurons form a laminar pattern of en passant terminal endings from ventromedial to dorsolateral within the ventrolateral regions of ICX, including the ventral border of IC, and the ventromedial edge of IC (or pericentral regions). These regions are collectively termed “the ventrolateral border region of ICX” (ICXV, (Zhou and Shore, 2006). The ICXV is the primary region that receives the convergent projections from CN and somatosensory systems, and thus is likely to be involved in multimodal integration in the IC (Shore, 2005; Jain and Shore, 2006).

Neurotransmitters used by somatosensory pathways to the CN

Studies using light and electron microscopy suggest that projections from both primary and secondary somatic sensory neurons to the VCN are excitatory (Wright and Ryugo, 1996; Shore et al., 2000; Zhou and Shore, 2004; Zhan et al., 2006). Mossy fibers in the CN that originate in the cuneate nucleus and Sp5 contain round synaptic vesicles and make asymmetric contacts with postsynaptic targets, features indicative of excitatory synapses (Wright and Ryugo, 1996; Haenggeli et al., 2005). The TG and C2 DRG terminals in the CN have similar ultrastructural characteristics (Shore et al., 2000; Zhan et al., 2006). The MFs from the cuneate nucleus are labeled with an antibody to glutamate, but not to choline acetyltransferase or GABA, thus also suggestive of a glutamatergic excitatory pathway (Wright and Ryugo, 1996).

Using double-labeling immunoreactivity techniques, Zhou et al. (2007) demonstrated that the Sp5 projection to CN is glutamatergic, and specifically uses vesicular glutamate transporter 2 (VGLUT2) to mediate glutamate transport at both its MF and small bouton terminal endings. VGLUTs selectively package glutamate into synaptic vesicles and mediate glutamate transport, and are therefore excellent markers of glutamatergic neurons. The expression of VGLUT1 and VGLUT2 is distinct in the CN: the most

intense VGLUT1 expression is in the magnocellular regions of the VCN and the molecular layer of the DCN, whereas the most intense expression of VGLUT2 is in the GCD (Zhou et al., 2007). Sp5 terminals colabel only with VGLUT2 in the GCD (Fig. 2) whereas, auditory nerve (AN) endings, including calyceal terminals, colabel only with VGLUT1 in the magnocellular regions of the VCN and deep layer of the DCN (Fig. 3).

The differential colocalization of VGLUT1 and VGLUT2 with AN and Sp5 terminals, respectively, suggests these are different forms of excitatory synaptic transmission that are dependent on the input source. Calyceal AN terminals are necessary for transmission of the acoustic signal with high temporal precision. Thus, VGLUT1 is

likely to be involved in fast transport of glutamate in the AN terminals in the CN in order to convey precise temporal information. The transfer of somatic sensory information to the CN, on the other hand, may be slow in nature. MFs in the cerebellum are able to adjust synaptic strength via enhanced neurotransmitter release (Sola et al., 2004). If a similar role in synaptic plasticity is played by MFs in the CN GCD, VGLUT2 may be associated with DCN synaptic plasticity via the Sp5 MF-to-granule cell connections. Plasticity changes in the pathways from Sp5 to CN under certain pathological conditions may then contribute to the enhanced activity of fusiform cells, and thus play a role in the initiation of tinnitus.

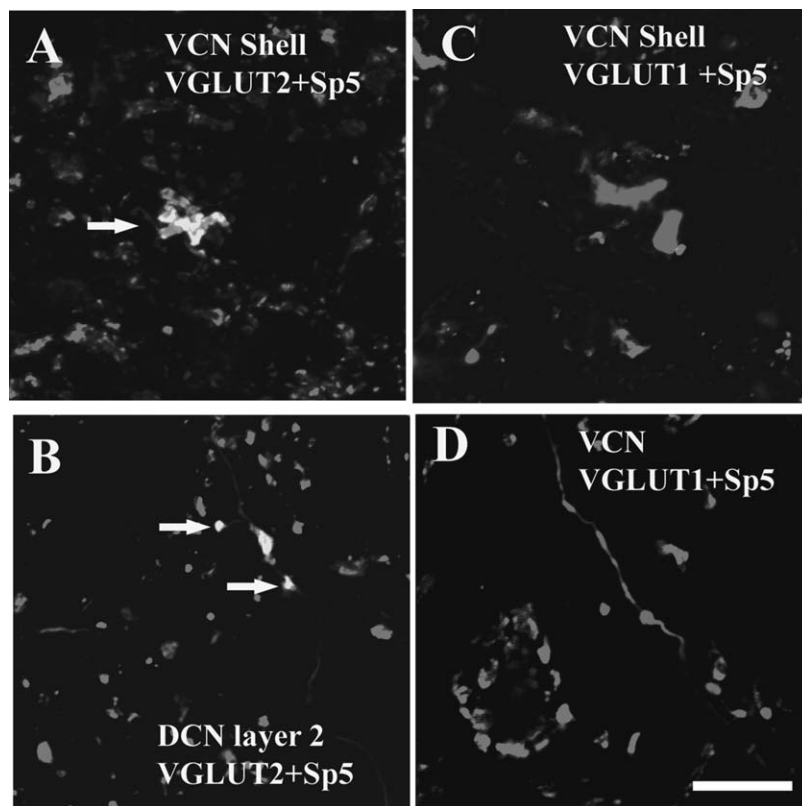


Fig. 2. High magnification confocal images ($63\times$) showing colocalization of anterogradely labeled Sp5 terminal endings with VGLUT2-ir in the CN. Green, VGLUT-ir. Red, Sp5 labeling. Yellow, double labeled terminals. Figures were obtained from Z projections of stacks of serial $1\mu\text{m}$ confocal images. (A) MFs are labeled with BDA from Sp5 and VGLUT2 in the shell region of the VCN (arrow). (B) Small boutons are labeled with BDA from Sp5 and VGLUT2 in the DCN layer 2 (arrows). (C and D) Sp5 terminal endings do not colabel with VGLUT1 in the shell region of the VCN and the core of the VCN. Scale bar = $10\mu\text{m}$ in D (applies to A–C). (See Color Plate 10.2 in color plate section.)

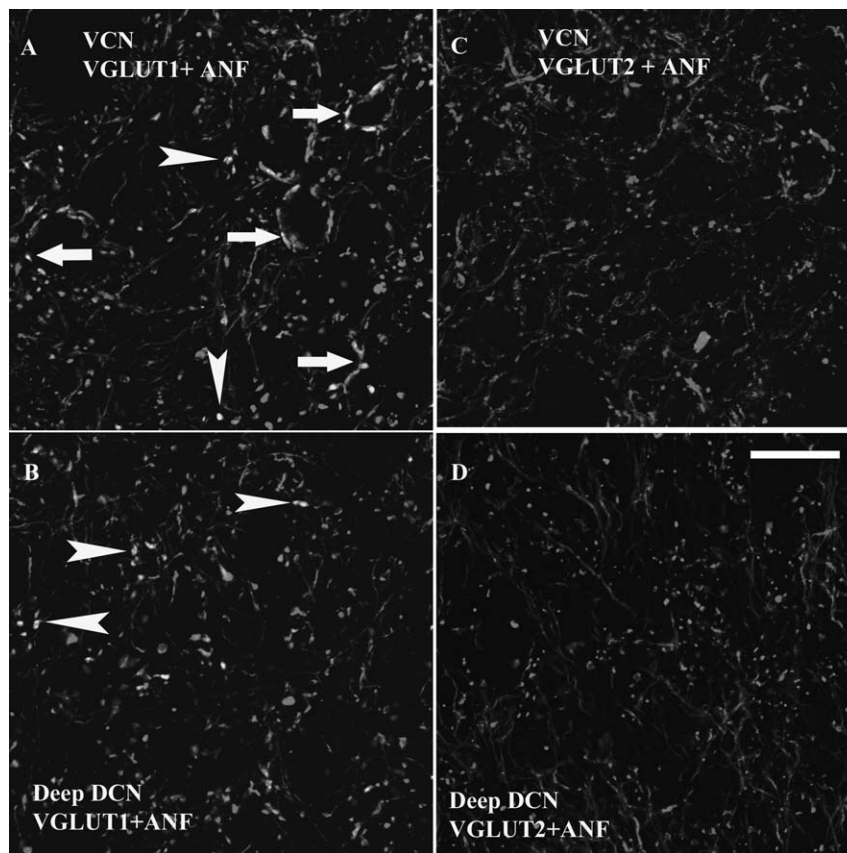


Fig. 3. High magnification 1 μ m confocal images ($63\times$) showing colocalization of AN terminal endings with VGLUT1-ir, but not VGLUT2-ir, in both the VCN and deep layer of the DCN. Green, VGLUT-ir. Red, FG filled AN fibers and endings. Yellow, double-labeled terminals. (A and B) Colocalization of AN terminal endings with VGLUT1-ir in VCN (A) and DCN layer 3 (B). Both endbulb-like AN endings (arrows in A) and small boutons (arrowheads in A and B) colabeled with the VGLUT1. (C and D) VGLUT2 did not label the AN endings in both VCN (C) and DCN layer 3 (D). Scale bar = 20 μ m in D (applies to A–C). (See Color Plate 10.3 in color plate section.)

Physiological substrates of somatic tinnitus

Physiological correlates of tinnitus in the auditory brainstem

Despite the likely contribution of peripheral factors, most comprehensive theories of tinnitus implicate central processes, especially in the CN. Increased *spontaneous rate* (SR) and *sound-driven* activity in DCN principal cells has been observed following noise-induced cochlear damage, and following ossicular disruption (Sumner et al., 2005), and has been proposed as a correlate of behavioral tinnitus in animal models

(Kaltenbach, 2000; Kaltenbach et al., 2000, 2002; Brozoski et al., 2002; Chang et al., 2002; Rachel et al., 2002; Zacharek et al., 2002). One mechanism for the increased SR could be a reduction in wideband inhibitory inputs from D-stellate cells in the VCN (Nelken and Young, 1994; Winter and Palmer, 1995) and narrowband inhibitory inputs from vertical cells to the fusiform cells (Nelken and Young, 1994; Zhang and Oertel, 1994; Davis and Voigt, 1997; Rhode, 1999; Salvi et al., 2000), essentially unmasking the excitability of the fusiform cells. Blocking glycine receptors increases sound-driven firing rate in fusiform cells, as indicated by the conversion of

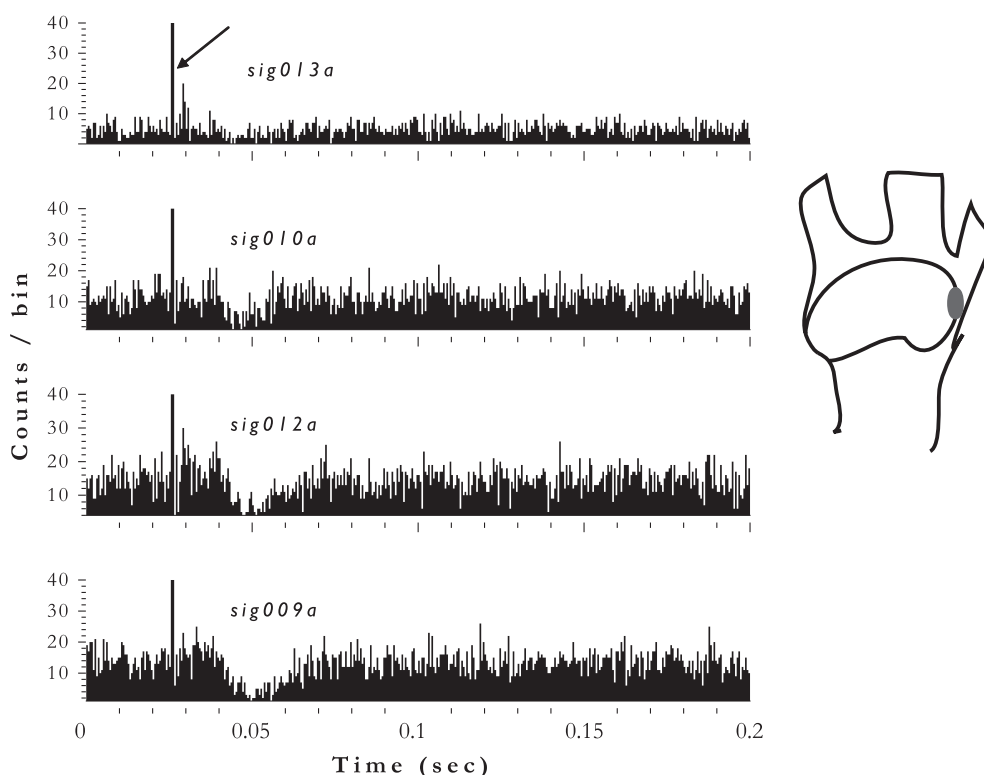


Fig. 4. Poststimulus time histograms of DCN unit responses to trigeminal ganglion stimulation show inhibition. Responses of four unit clusters from 4 channels (9, 10, 12, 13) of 16-channel electrode are shown. Stimulation was at $80\mu\text{A}$, 100 ms/phase bipolar pulses, 100 presentations. Bin width, 0.5 ms. Arrow — electrical stimulus artifact indicates onset of TG stimulation. Inset at right shows location of the stimulating electrode in the ophthalmic region of the TG.

nonmonotonic to monotonically rising rate-intensity functions for BF tones (Caspary et al., 1987; Davis and Young, 2000). This could account for the increase in spontaneous and sound-driven responses observed following noise trauma, giving rise to a tonal perception near to the affected frequency (Brozoski et al., 2002).

Another mechanism that could give rise to the percept of a tonal tinnitus is an increased *regularity* in the firing patterns of affected neurons. In support of this hypothesis, an increase in correlated SRs of simultaneously recorded cells in auditory cortex was reported following quinine administration, as well as a change in the best modulation frequency in response to AM signals (Ochi and Eggermont, 1997). While temporal changes following noise trauma have not been explored in the DCN, one study reported an

increased bursting activity of DCN cells following acoustic trauma (Chang et al., 2002).

Thus, in order for somatosensory neurons to alter the intensity and the character of tinnitus, they would have to either alter the spontaneous (i.e., not driven by auditory stimuli) rates, or the synchrony of firing among neurons in the CN, IC, or auditory cortex. Here we will concentrate on the effects of activating somatosensory neurons on neural activity in the CN and IC.

Effects of trigeminal nerve activation on CN activity

Effects on spontaneous rates of CN neurons

Current pulses delivered to the ophthalmic divisions of the TG, at the origins of projecting

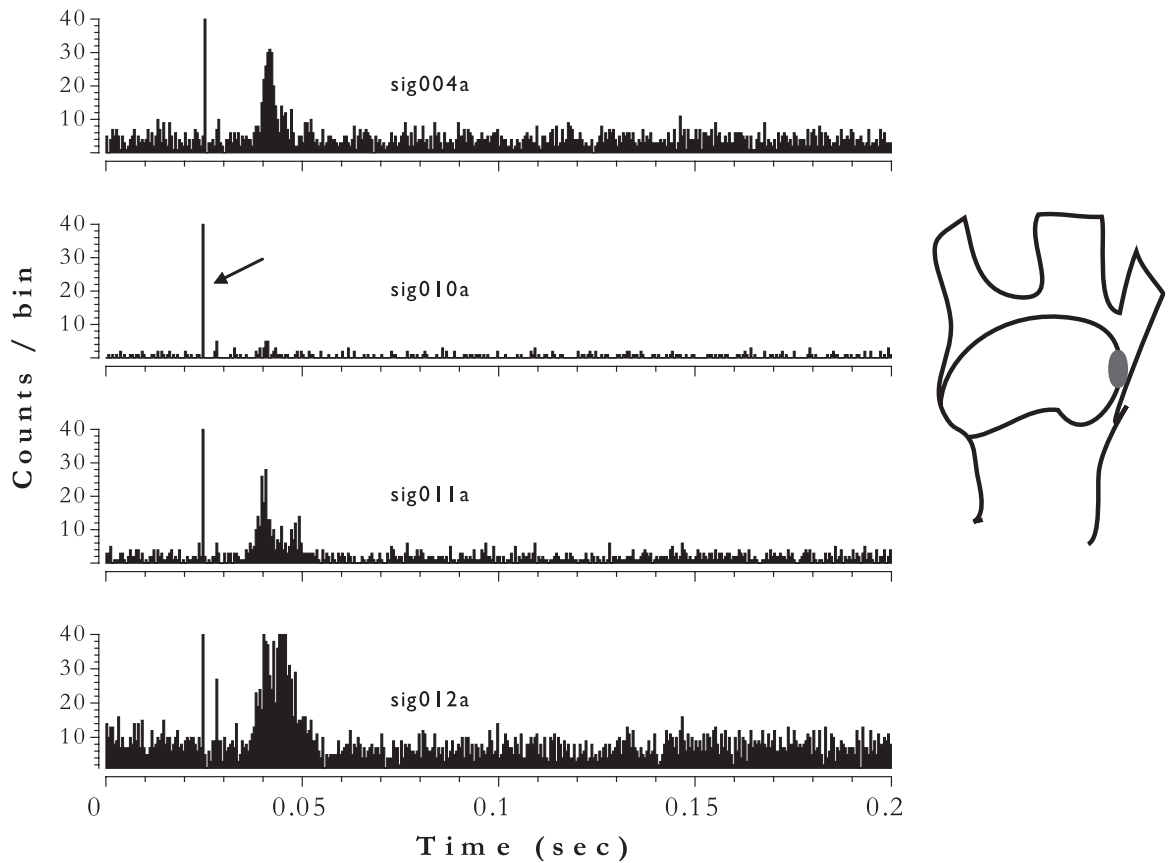


Fig. 5. Poststimulus time histograms of DCN unit responses to trigeminal ganglion stimulation show excitation. Responses of four different unit clusters from 4 channels (4, 10, 11, 12) of a 16-channel electrode in the same animal but different penetration as for Fig. 4, are shown. Stimulation was at $80\ \mu\text{A}$, 100 ms/phase bipolar pulses, 100 presentations. Bin width, 0.5 ms. Arrow — electrical stimulus artifact indicates onset of TG stimulation. Inset at right shows location of the stimulating electrode in the ophthalmic region of the TG.

neurons to the CN (Shore et al., 2000), can excite neurons in the VCN (Shore et al., 2003) and excite or inhibit neurons in the DCN (Shore, 2005; Shore and Zhou, 2006). Figure 4 shows the responses recorded from four channels of a 16-channel recording electrode in the DCN. The onset of the electrical stimulus in the TG is evident as stimulus artifact at 25 ms. Strong inhibitory responses are achieved on three of the four channels. The latencies of these responses are around 12 ms for these recordings but can range from 5 ms to 20 ms, reflecting the multisynaptic pathways that are necessarily stimulated at the origin of the central projections from the trigeminal nerve (Shore, 2005). Figure 5 shows an example of excitatory

responses recorded from four different channels on the same multichannel electrode in the same animal (see Fig. 6 for electrode configuration). Whether the units are activated or inhibited depends on the location and type of unit rather than on the location of the stimulating electrode. Thus, activity in trigeminal pathways to the CN can alter the spontaneous (i.e., non-sound-driven) activity of neurons in both the VCN and the DCN. Change in the *firing rate* of CN neurons by incoming trigeminal neurons could be one means by which the *loudness* of tinnitus is modulated in individuals with somatic tinnitus changing the *synchrony* between neurons could be a mechanism for altering the *pitch* of the tinnitus.

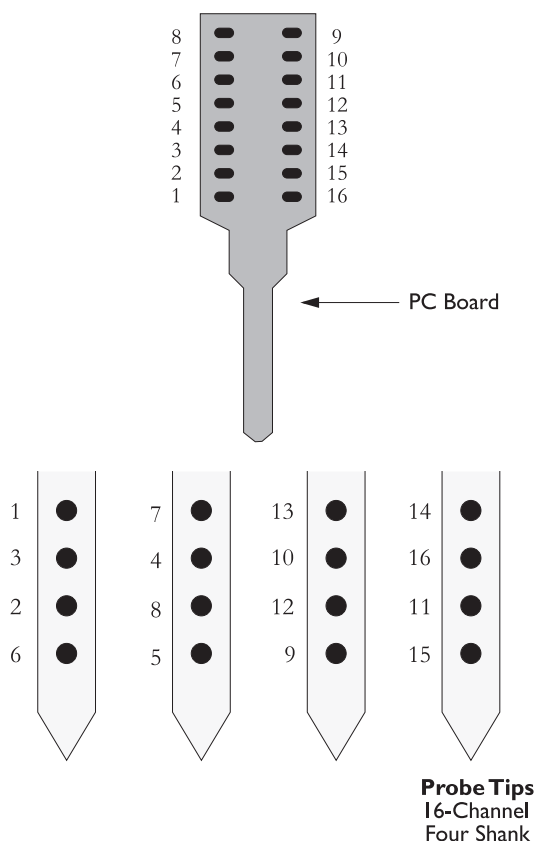


Fig. 6. Configuration of the multichannel electrode used to record responses shown in Figs. 3 and 4. The four shank, 16-channel electrodes are positioned on the dorsal aspect of the DCN and lowered into the fusiform cell layer (layer 2) of the DCN. Often responses from multiunit clusters are recorded from each channel, which are then sorted using the Plexon offline sorter, into single units.

Effects of trigeminal stimulation on sound-driven rates of CN neurons

Since tinnitus is manifest as an increase in SR, it may be valid to examine the effects of somatosensory inputs on firing rates driven by low levels of sound, simulating a 'greater than normal' firing activity (as in tinnitus).

Stimulating the TG has more complicated effects on sound-evoked responses of CN neurons. In some cases, preceding an acoustic stimulus with a current pulse to the TG causes the sound-evoked activity of DCN neurons to decrease (Fig. 7A). The closer in time the two stimuli are, the more

pronounced the suppression. Note that the response to the TG stimulation itself (depicted by the arrow) in these examples is excitatory, as is the response to the sound. The combination of the two signals results in a suppression of the response to the sound. This is an example of *multisensory integration* in which the response to stimulation of both senses results in a nonlinear combination of the responses from each system. Figure 7B shows how the response rate of unit 16 to the sound is most depressed when the trigeminal stimulus is closest to the sound (Δt , $\Delta t = 20$ ms), and is less depressed as the stimuli are separated in time. Note that the response of unit 16 to a BF toneburst is "pauser-buildup," the typical response pattern of pyramidal cells. This figure also shows the responses from two other units (5a and 5b) that are less affected by the trigeminal stimulus. Responses of unit 5b to sound are slightly suppressed at mid Δt values. The response type for unit 5b is typical of that shown for cartwheel cells (Parham and Kim, 1995).

In some neurons, the addition of the TG pulse before the sound can *enhance* rather than suppress the response to the sound (Fig. 8). Note in this case that the response to the preceding TG pulse is inhibitory, i.e., suppresses SR. In these examples, when the response to TG stimulation is inhibition, the combined response is enhancement and when the response to TG stimulation is excitation, the combined response is suppression.

Effects of dorsal root ganglion and dorsal column activation on DCN activity

Somatic tinnitus includes the modulatory effects of neck and upper limb manipulation on the pitch and loudness of tinnitus. Physiologically, this may correspond to modulation of neural activity in the DCN by activation of the dorsal column nuclei and cervical DRG.

Evoked potentials

Stimulation of cervical nerves can elicit evoked potentials in the DCN. The evoked potentials are largest in response to stimulation of the cervical

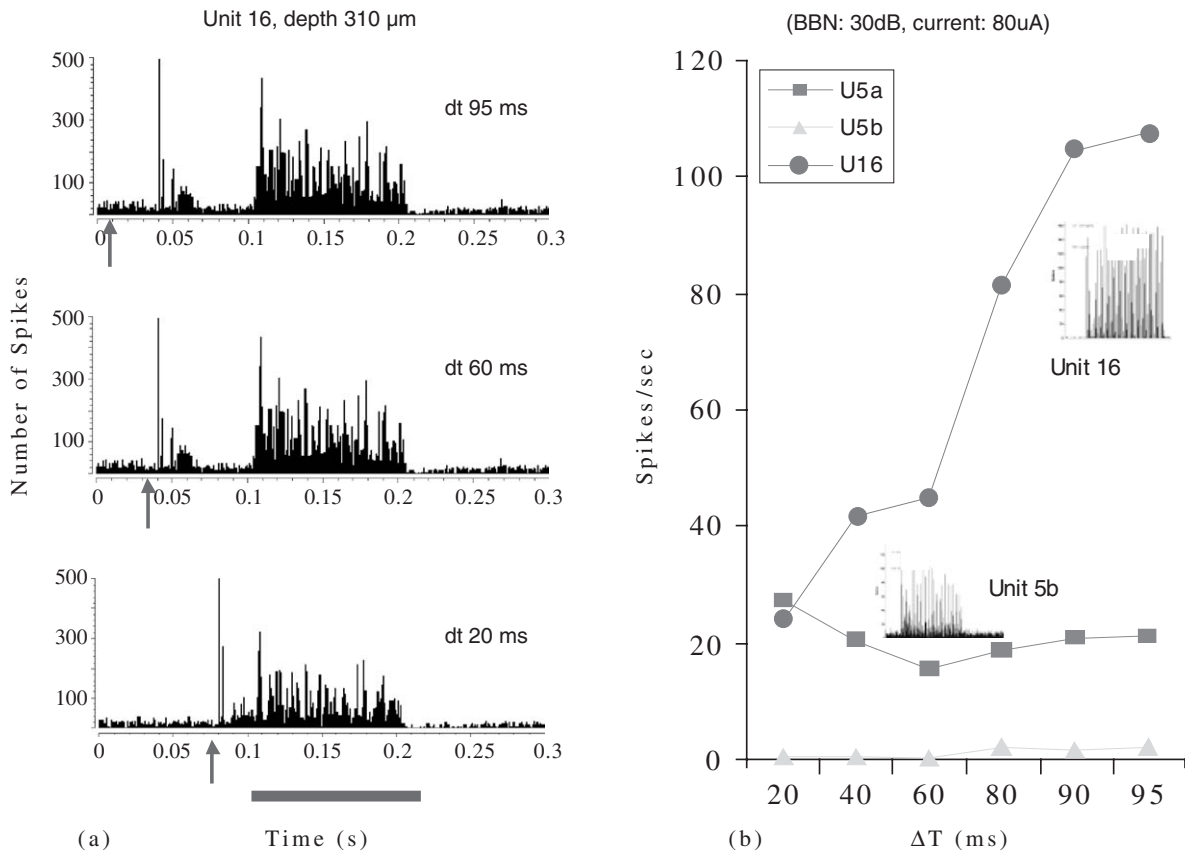


Fig. 7. (A) Poststimulus time histograms of a DCN single unit's response to TG stimulation combined with acoustic stimulation. The TG pulse precedes the acoustic stimulus (broadband noise at 30 dB SPL) by varying amounts designated by dt. Acoustic stimulus duration is indicated by red bar below histograms. Arrow indicates onset of TG pulse (80 μA , 100 ms/phase bipolar pulses, 100 presentations). Responses to three different dt values are shown. Preceding the acoustic stimulus by TG stimulation results in a diminished response to the acoustic stimulus. The effect is stronger when the two stimuli are closer. Bin width, 0.5 ms. Arrow — electrical stimulus artifact indicates onset of TG stimulation. (B) Quantification of the spike rates achieved in (a) for unit 16. Spike rates for two other units, 5a and 5b, are also shown. Insets: Poststimulus time histograms for responses to BF tonebursts indicate unit types; Unit 16 is a P-Buildup; Unit 5b may be a cartwheel cell.

nerves corresponding to mechanoreception and proprioception in the pinna (C2), neck (C7), and forelimbs (C8) (Kanold and Young, 2001), similar to those evoked by TG stimulation (Shore et al., 2003). In addition, stimulation of the femoral nerve can activate cells in the DCN as evidenced by Fos expression (McKittrick and Calaresu, 1993).

Single unit responses

Activation of dorsal column nuclei with current pulses elicits excitatory and inhibitory single unit

responses in the DCN: responses of DCN units have both short- and long-latency inhibitory phases and a transient excitatory phase (Young et al., 1995). The transient excitatory peak can be facilitated by multiple pulses, while the long-latency inhibition can be suppressed by multiple pulses. Single unit responses in the DCN to electrical activation of the DRG are similar to responses to activation of the dorsal column nuclei but with longer latencies (Kanold and Young, 2001). In addition, dorsal column stimulation can alter sound-evoked responses in a

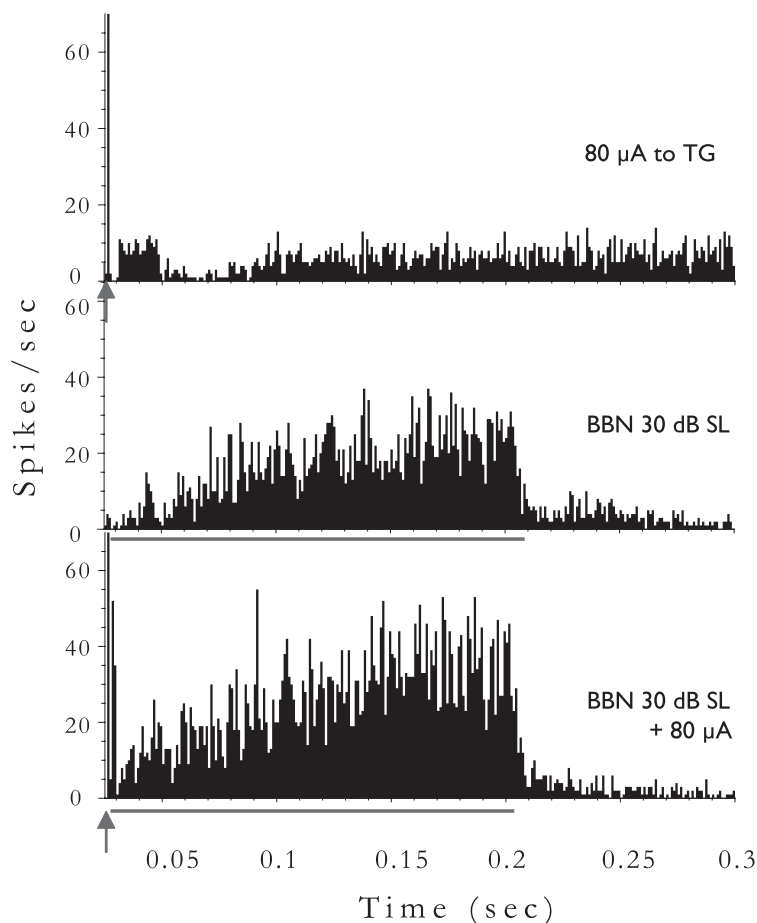


Fig. 8. Poststimulus time histograms of a different DCN single unit's response to TG stimulation combined with acoustic stimulation. The TG pulse precedes the acoustic stimulus (broadband noise at 30 dB SL) by 5 ms. Acoustic stimulus duration is 200 ms, indicated by red bar below histograms. Arrow indicates onset of TG pulse ($80\text{ }\mu\text{A}$, 100 ms/phase bipolar pulses, 100 presentations). In this unit, preceding the acoustic stimulus by TG stimulation results in an enhanced response to the acoustic stimulus. Note, the buildup pattern of response indicates that this cell was likely a pyramidal cell.

similar manner to that described above for trigeminal stimulation (Saade et al., 1989; Kanold et al., 2001), producing bimodal integration.

How could this bimodal integration occur? Figure 9 shows a schematic of the DCN circuitry including AN and somatosensory inputs. Somatosensory stimulation activates granule cells (gr), which excite the principal output neurons of the DCN, fusiform (fu), or giant (gi) cells, as well as inhibitory interneurons, the cartwheel (ca) cells (Golding and Oertel, 1997) and stellate cells (st). Cartwheel and stellate cells, in turn, inhibit principal cells (Davis et al., 1996). Sound stimulation

(via AN fibers, a.n.f.) strongly excites fusiform cells (Stabler et al., 1996; Young, 1998) and weakly excites cartwheel cells (Parham and Kim, 1995). Suppression of sound-evoked responses of fusiform or giant cells could be achieved by the summation of weak responses from cartwheel cells to sound and stronger cartwheel cell responses to trigeminal input, leading to inhibition of the principal cell response to sound. Similarly, facilitation of responses to sound could occur through summation of granule cell — fusiform/giant cell activation by sound and trigeminal input. Somatosensory stimulation can precede acoustic

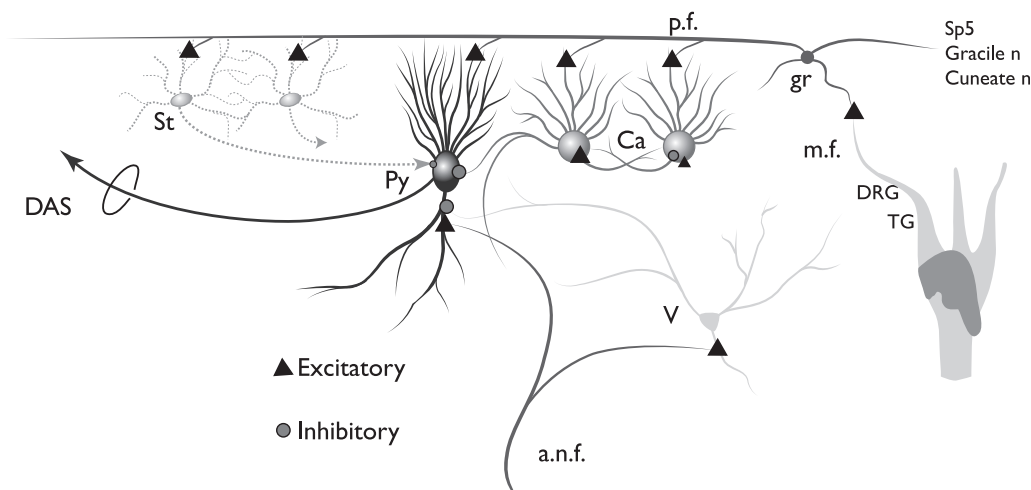


Fig. 9. Schematic of DCN circuitry. Pyramidal cells (Py) in layer II of the DCN receive inputs on their basal dendrites from auditory nerve fibers (a.n.f.) and vertical (v) cells. The apical dendrites of the pyramidal cells receive inputs from the parallel fiber axons (p.f.) from granule cells (gr) in the VCN, while their cell bodies receive inputs from cartwheel (Ca) and superficial stellate (st) cells. Projections from the trigeminal ganglion (TG), spinal trigeminal nucleus (Sp5), dorsal column nuclei (Gracile and cuneate n), and the dorsal root ganglion (DRG), synapse on granule cells. (See Color Plate 10.9 in color plate section.)

stimulation by up to 90 ms and still alter the firing rate to acoustic stimulation for the duration of the sound stimulus (Shore, 2005).

Effects of Sp5 activation on IC activity

Single unit recordings from ICX reveal that trigeminal stimulation can suppress SRs as well as produce bimodal integration of the type described above in the DCN (Shore, 2005; Jain and Shore, 2006). Units in both locations show mostly suppression, but also show enhancement of acoustically driven responses by trigeminal stimulation. Figure 10 shows two examples of suppression of spontaneous and sound-driven responses in ICX neurons by trigeminal stimulation. In these experiments, the trigeminal stimulation site was in Sp5. The top graph shows a nonmonotonically increasing rate-level response to sound stimulation (broadband noise), decreasing at high levels. The effects of Sp5 stimulation at several current levels are to suppress the SRs as well as the responses to sound especially at low sound levels (20 dB SPL). The bottom graph shows similar effects for a monotonically decreasing rate-level function: Sp5 stimulation further decreases the response to sound around 20 dB SPL. Greater suppression of

SR occurs in the lower unit. The importance of this study is its demonstration that the effects on SRs as well as bimodal processing initiated in the DCN are passed on to the next level to be integrated by the extra-lemniscal system.

How do responses of DCN and IC neurons to combined sensory stimulation relate to somatic tinnitus? The suppression or enhancement of sound-evoked activity in DCN and ICX could be analogous to the suppression or enhancement of tinnitus experienced by some individuals with tinnitus. Maneuvers that alter the tinnitus such as clenching of the jaw or lateral gaze would be analogous to electrical stimulation of the TG or Sp5, as described above, that alters the neurons' spontaneous activity or responses to sound. The underlying mechanisms for these alterations could involve long-term depression (LTD)/potentiation (LTP). Such long-term plasticity of synapses occurs between parallel fibers and their targets, the fusiform, giant, and cartwheel cells. When postsynaptic depolarization is preceded by stimulation of parallel fibers in slice experiments, LTP or LTD is produced in fusiform and cartwheel cells (Fujino and Oertel, 2003; Tzounopoulos et al., 2004). Parallel fiber inputs to fusiform cells are *strengthened* (LTP) when paired with subsequent postsynaptic firing, whereas in

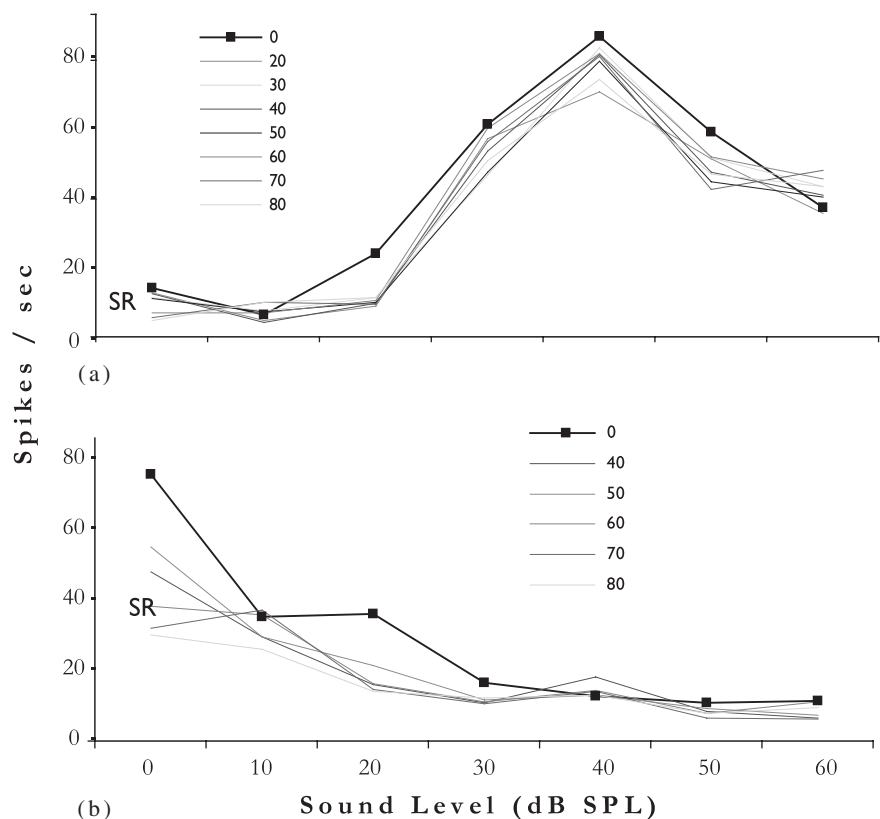


Fig. 10. Rate-level functions for two different units in ICx (A and B) in response to broadband noise stimuli (100 ms, 5 ms rise/fall times) with and without Sp5 stimulation. Trigeminal stimulus was at the onset of the acoustic stimulus. Response to Sp5 stimulation alone was minimal, but Sp5 stimulation reduced the responses of units in A and B to sound stimulation. The effects were more pronounced at low sound levels. (Adapted with permission from Jain and Shore, 2006.) (See Color Plate 10.10 in color plate section.)

cartwheel cells they are *weakened* (LTD) (Tzounopoulos et al., 2004). The induction of LTP in fusiform cells and LTD in cartwheel cells has the net effect of increasing the firing rates of fusiform cells because cartwheel cells provide feed-forward inhibition to fusiform cells. Reversing the order of pre- and postsynaptic activation produces LTD in fusiform cells, but does not change LTD to LTP in cartwheel cells, resulting in a net depression of firing rate in fusiform cells.

Another mechanism that could contribute to these effects is activation of GABA_B receptors in the DCN that regulate dendritic excitability and excitatory inputs (Caspari et al., 1987). GABA_B receptors in CN are indeed strategically placed to modulate glutamatergic neurotransmission between the granule cells and their targets, the

fusiform, cartwheel, and stellate cells in the superficial layers. The sources of GABAergic inputs to these regions could be vertical cells or superficial stellate cells, which cocontain GABA as well as glycine (Mugnaini, 1985; Altschuler et al., 1991; Davis and Young, 2000). These mechanisms would be reflected also in neurons in the ICX that receive direct inputs from DCN neurons. Additional processes within the IC may enhance the effects already evident at the level of the DCN.

Abbreviations

CN	cochlear nucleus
DCN	dorsal cochlear nucleus
DRG	dorsal root ganglion

GCD	granule cell domain
IC	inferior colliculus
ICX	external cortex of IC
MF	mossy fiber
PSTH	poststimulus time histogram
Sp5	spinal trigeminal nucleus
Sp5C	caudal spinal trigeminal nucleus
Sp5I	interpolaris spinal trigeminal nucleus
SR	spontaneous rate
TG	trigeminal ganglion
VCN	ventral cochlear nucleus
VGLUT	vessicular glutamate transporter

Acknowledgments

This work supported by grants from the National Institutes of Health (R01 DC 004825; P30 DC 05188), Tinnitus Research Consortium, Tinnitus Research Initiative and American Tinnitus Association. We thank Sana Syed and Naveen Nannapaneni for technical assistance and Ben Yates for graphic design and technical writing assistance.

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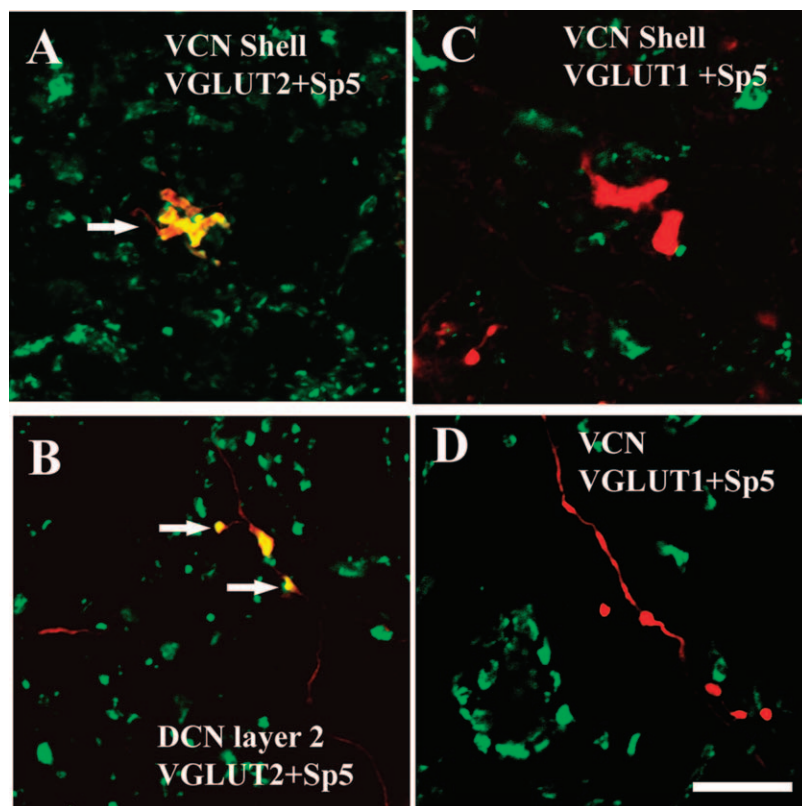


Plate 10.2. High magnification confocal images ($63\times$) showing colocalization of anterogradely labeled Sp5 terminal endings with VGLUT2-ir in the CN. Green, VGLUT-ir. Red, Sp5 labeling. Yellow, double labeled terminals. Figures were obtained from Z projections of stacks of serial $1\mu\text{m}$ confocal images. (A) MFs are labeled with BDA from Sp5 and VGLUT2 in the shell region of the VCN (arrow). (B) Small boutons are labeled with BDA from Sp5 and VGLUT2 in the DCN layer 2 (arrows). (C and D) Sp5 terminal endings do not colabel with VGLUT1 in the shell region of the VCN and the core of the VCN. Scale bar = $10\mu\text{m}$ in D (applies to A–C). (For B/W version, see page 112 in the volume.)

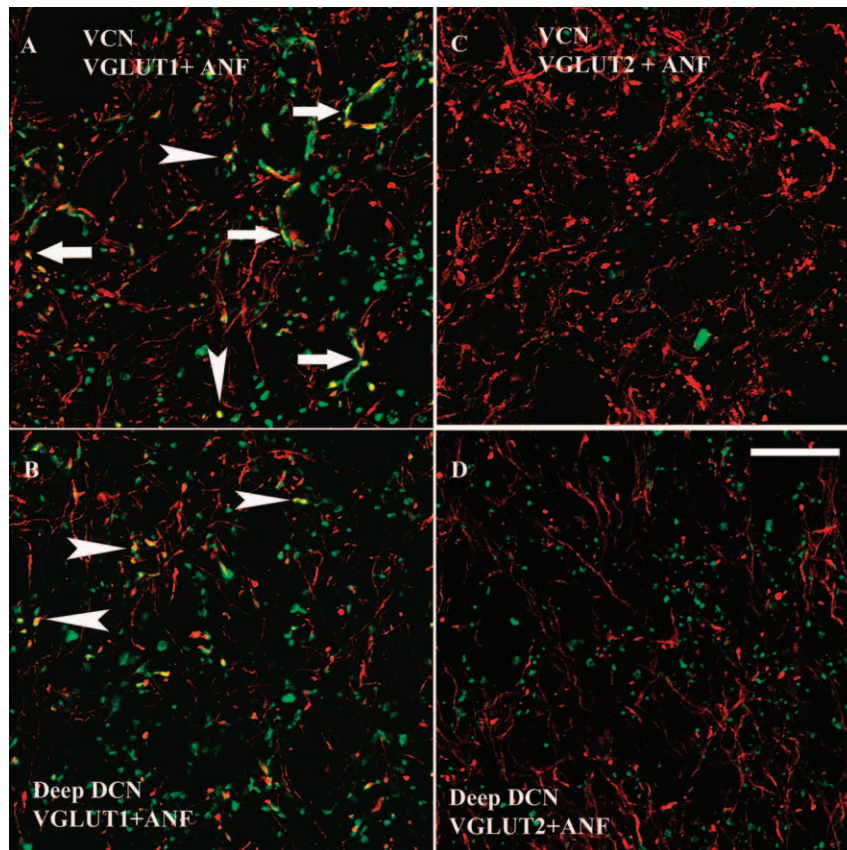


Plate 10.3. High magnification 1 μ m confocal images ($63\times$) showing colocalization of AN terminal endings with VGLUT1-ir, but not VGLUT2-ir, in both the VCN and deep layer of the DCN. Green, VGLUT-ir. Red, FG filled AN fibers and endings. Yellow, double-labeled terminals. (A and B) Colocalization of AN terminal endings with VGLUT1-ir in VCN (A) and DCN layer 3 (B). Both endbulb-like AN endings (arrows in A) and small boutons (arrowheads in A and B) colabeled with the VGLUT1. (C and D) VGLUT2 did not label the AN endings in both VCN (C) and DCN layer 3 (D). Scale bar = 20 μ m in D (applies to A–C). (For B/W version, see page 113 in the volume.)

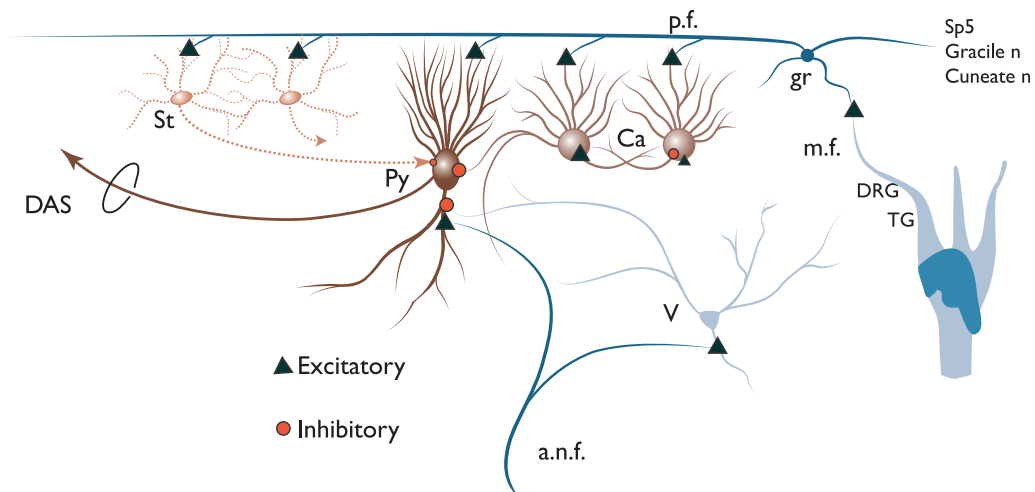


Plate 10.9. Schematic of DCN circuitry. Pyramidal cells (Py) in layer II of the DCN receive inputs on their basal dendrites from auditory nerve fibers (a.n.f.) and vertical (v) cells. The apical dendrites of the pyramidal cells receive inputs from the parallel fiber axons (pf) from granule cells (gr) in the VCN, while their cell bodies receive inputs from cartwheel (Ca) and superficial stellate (st) cells. Projections from the trigeminal ganglion (TG), spinal trigeminal nucleus (Sp5), dorsal column nuclei (Gracile and cuneate n), and the dorsal root ganglion (DRG), synapse on granule cells. (For B/W version, see page 119 in the volume.)

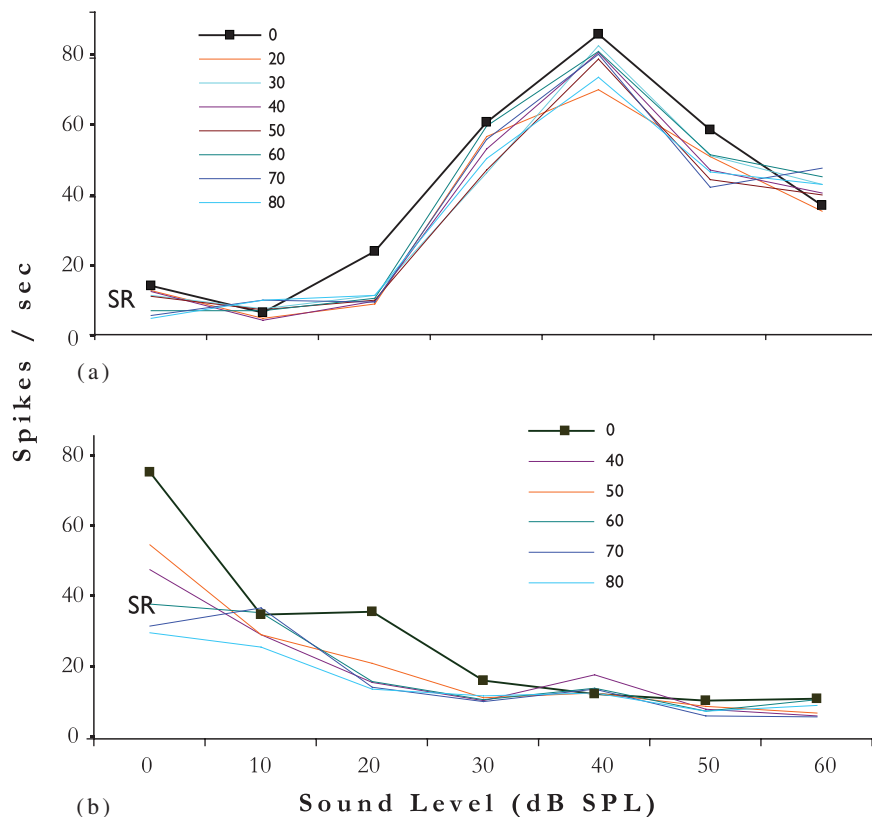


Plate 10.10. Rate-level functions for two different units in ICx (A and B) in response to broadband noise stimuli (100 ms, 5 ms rise/fall times) with and without Sp5 stimulation. Trigeminal stimulus was at the onset of the acoustic stimulus. Response to Sp5 stimulation alone was minimal, but Sp5 stimulation reduced the responses of units in A and B to sound stimulation. The effects were more pronounced at low sound levels. (Adapted with permission from Jain and Shore, 2006.) (For B/W version, see page 120 in the volume.)

CHAPTER 11

Neural network models of tinnitus

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Abstract: In this chapter we review the relatively recent effort on the part of neuroscientists to use computational neural network modeling to investigate the neural basis of subjective tinnitus. There are advantages and challenges in using a modeling framework to understand this complex auditory disorder. The foremost challenge to modeling a subjective condition such as tinnitus is the evaluation of the occurrence of tinnitus in the model. We propose comparing measures of the model's activities (simulated neuronal activity, behavioral activity, or neuroimaging activity) with experimental data obtained from studies of tinnitus in humans and animals; strong agreement with experimental data will provide support for the validity of the simulation of tinnitus in a particular model. A major advantage of neural network modeling is that it allows experimentation not possible in animals. Models make it possible to evaluate the contribution of different neural mechanisms affecting tinnitus in a principled manner. A model makes predictions that can be tested by experiments thus leading to the designing of focused experiments. We review several neural models of tinnitus and discuss published findings from simulations using these models. We conclude with a proposed scheme for investigating tinnitus that combines neural network modeling with brain imaging experiments.

Keywords: neuroimaging; electrophysiological; fMRI; auditory; cerebral cortex; thalamus

Introduction

In this chapter we will discuss the application of a technique known as neural network modeling to investigate the neural sources and mechanisms of tinnitus. The type of tinnitus considered for modeling is subjective, central tinnitus. Subjective tinnitus is characterized by the phantom perception of sounds in the absence of an external acoustic source. It is a consequence of self-generated

abnormal neural activity (Jastreboff, 1990; Møller, 2006).

This chapter begins with a brief introduction to modeling, specifically neural network modeling, and then describes the advantages of applying this technique toward the understanding of the neural bases of tinnitus. Several neural models of tinnitus are reviewed and their advantages and weaknesses discussed with respect to the available evidence regarding tinnitus. We describe some of the challenges, and schemes that can be used to resolve these challenges, in assessing the occurrence of tinnitus in a model. The chapter concludes with a proposed scheme for modeling tinnitus that brings together state-of-the-art techniques in neural network modeling and in brain imaging. We will

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abbreviate “computational or mathematical modeling” by “modeling;” any other type of modeling (e.g., animal modeling) will be specifically noted.

A primer on modeling

Modeling, in the most abstract sense, provides a framework within which to *explicitly* state assumptions and articulate hypotheses. A useful model makes explicit predictions that can be tested. A mathematical or computational model differs from a theoretical, descriptive model in that the assumptions are articulated via mathematical rules. The rules may be instantiated via construction of one or more modules (independent, self-contained components of a model) that incorporate such rules, and their connection and activation patterns. A model, by definition, captures a few important dimensions of the phenomenon being studied, thus allowing for the interpretation of the phenomenon using the reduced data set.

“Neural modeling” refers to the modeling of brain function via different computational schemes (Arbib, 2003). For reviews about neural modeling see Horwitz et al. (2000) and Husain and Horwitz (2006). A neural network consists of several interconnected modules or elements that execute some mathematical function (often representative of a neural mechanism). The connections can be weighted and are excitatory or inhibitory in nature. They transfer activity from one module to another. However, a single module does not generate the functionality realized by the entire network; rather, the complex input–output relationship realized in the model is an emergent property arising out of the workings of the modules and their connections.

Models can be described and distinguished from each other based on a number of attributes. Typically the attributes are not binary but vary along a continuum. One distinguishing feature of a model is whether it uses a simulation or a data-fitting approach to represent the data. In a simulation approach, a model is constructed (i.e., a set of model parameters is defined and values for each parameter are assigned) and data are generated

from the model. These data are then compared with appropriate experimental data and the model is considered successful if there is close agreement between the experimental and simulated data. In a data-fitting approach, some computational procedure is used to vary the model parameters until there is agreement between experimental data and data generated by the model. Examples of data-fitting modeling are provided by Goncalves et al. (2001) and Maddox et al. (2002) and of simulation modeling by Grossberg and Myers (2000) and Husain et al. (2005). The distinction between simulation and data-fitting models is not clear-cut, but often data-fitting models are less specific and detailed about the meaning of the model parameters than are simulation models. Frequently, the parameters used in simulation models are based on a different set of data than on the data to which the model is being applied, whereas the values of the parameters used in data-fitting models are not.

Another attribute used to describe neural models is that of biological plausibility. The more neurobiologically realistic models attempt to simulate neural mechanisms explicitly. Such models frequently start with modules that realize lower-level (lower can mean such things as more fundamental, more microscopic, more basic, e.g., neural level) mechanisms and use these building blocks to generate higher-level (e.g., cognitive level) functionality. The higher-level phenomenon being explained emerges from the architecture and mechanisms being implemented at a lower level (e.g., Husain et al., 2004). The less neurobiologically realistic models typically take a top-down approach to model the brain regions implementing cognitive mechanisms (e.g., Just et al., 1999; Anderson et al., 2003). In these models, although the output of the model can be matched against human experimental data (such as behavioral measures), there is less of an attempt to match the functioning of the individual elements of the model to neural mechanisms. This is not to say that the less neurobiologically realistic models do not contribute as much as the more biologically plausible ones to our understanding of a given phenomenon. The type of model one considers developing depends on the objective. For instance, because of the lack of neural-level data of a

cognitive phenomenon such as the pragmatics of reading a paragraph, a model of such a task will necessarily be less biologically realistic (compared to a model, e.g., of processing of sounds in the auditory nerve), yet can add to our understanding of the phenomenon.

Beginning in the early 1990s, investigators started using various neural network models to interpret functional brain imaging data (e.g., McIntosh and Gonzalez-Lima, 1991; Friston, 1994; Horwitz and Sporns, 1994; Arbib et al., 1995; Tagamets and Horwitz, 1998). Functional brain imaging methods are relatively non-invasive and can be performed in humans making it possible to investigate some aspects of the neural basis of conditions reported uniquely by humans such as language or subjective tinnitus (for a review, see Frackowiak et al., 2004). In contrast to electrophysiological or lesion data that focus on a single neural entity (e.g., neurons or brain regions) at a time, hemodynamic-based functional brain imaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) have the ability to provide information about brain activity from essentially all brain regions simultaneously during the performance of cognitive tasks. These techniques typically have a spatial resolution ranging from several millimeters to 1–2 cm and a temporal resolution of few seconds to a minute (for PET, the temporal resolution is ~30–60 s; for fMRI, it is generally of the order of 1–3 s), and are inferior to the resolution of neuronal activity along both spatial and temporal dimensions. Other techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG) are also used, and these methods generate good temporal information, but spatial localization is less well defined than is the case for fMRI and PET (see Horwitz et al., 2000). The different types of data (electrophysiological, functional neuroimaging, etc.) provide us with some information about the neural basis of a cognitive function, but along different temporal, spatial, and featural dimensions, and there is no easy and straightforward way to put all these types of information together. Horwitz et al. (1999) have argued that computational neural modeling provides a method by which all relevant

neuroscientific data pertaining to a cognitive task or a disorder can be accounted for in terms of the dynamic interactions of multiple neuronal populations. For instance this may mean that one can account for hemodynamic-based brain imaging data with a spatial resolution of a few millimeters in terms of the activity of the underlying neurons in a biologically realistic bottom-up fashion (e.g., Husain et al., 2004).

In a complex disorder such as tinnitus, with its varying and often uncertain and sometimes multiple etiology, and varying range and severity of the symptoms, and where the evidence is obtained from different sources such as single cell recordings in animals and brain imaging data from humans, neural network modeling becomes essential in order to provide a common framework to account for these diverse data and to develop a cogent theory. A biologically realistic neural network model of tinnitus may simultaneously account for electrophysiological, behavioral, or neuroimaging data from animal and human studies of tinnitus. Such a model can be used to evaluate the capability of different neural mechanisms responsible for generating or modulating tinnitus. Thus, the use of neural network modeling offers several possibilities for advancing our knowledge about tinnitus.

Advantages in modeling the generation of tinnitus

The most common use of modeling is to state clearly the assumptions (e.g., the sources and mechanisms of tinnitus) and to make predictions that lead to more focused experiments. In the context of tinnitus it means that models of, for instance, likely mechanisms generating tinnitus would be of value, as would models that could suggest what experiments should be done. Although we do not know enough about the neural mechanisms of tinnitus in order to completely constrain a neural network model, development of models is worthwhile because modeling may teach us something about how tinnitus could be generated and it may lead to new hypotheses and more productive experimentation. A model can reduce data complexity by focusing only on a few possible

sources of tinnitus, allowing for the interpretation of the phenomenon based on this reduced data set, and leading to the development of testable predictions. Focused experiments can then be designed to test these predictions.

One benefit of modeling is that it can evaluate the contribution of different neural mechanisms affecting tinnitus in a principled fashion. A single model can simulate different scenarios using different biological mechanisms (individual parameters) and match the simulated output data (e.g., neuronal activity or neuroimaging data) with the experimental data. Additionally, several different models can be generated (by varying pathways and modules) to test the effects of neural plasticity, and simulated data from each model matched with the experimental data to find the most probable model. Such evaluations in turn can help us create hypotheses about, for instance, how tinnitus arises in some individuals with hearing loss and not in other individuals with similar hearing loss. This in turn can lead to experiments specifically designed to test these hypotheses, thus expanding our understanding of tinnitus.

A similar modeling-experimental scheme has been used successfully to identify which of a number of candidate maturational mechanisms are most influential in the development of working memory capacity during childhood (Edin et al., 2007; see also Macoveanu et al., 2006). The cellular maturational processes underlying the development of working memory capacity are still unknown, although, there are a number of possible candidates such as myelination, synaptic strengthening, and synaptic pruning. In order to distinguish between processes that improved working memory and those that did not, the investigators implemented developmental changes occurring due to the different mechanisms using as their starting point a previously developed biologically realistic network model (Tegner et al., 2002). The developmental changes in memory activity predicted from the different model simulations were compared to the brain activity measured from experimental fMRI studies in children and adults. The results showed that only one mechanism, namely, stronger synaptic connectivity between the frontal and parietal

cortices, could account for the experimental data.

Another advantage of modeling is that it allows us to investigate the effects of new therapies. One such therapy is that of transcranial magnetic stimulation (TMS) (see Chapters 34 and 35). TMS is a technique in which a strong focal magnetic field is applied to a region on the human scalp inducing electric currents in the brain. These currents influence regional neuronal function. Repetitive TMS (rTMS) has recently been introduced as a method to treat patients with tinnitus (Eichhammer et al., 2003; Langguth et al., 2003). In these studies, low-frequency rTMS is applied to the auditory cortices and results in decreased tinnitus after a period of treatment, but the exact mechanisms responsible for the decrease in the tinnitus are unknown. Further, animal studies, which could help inform us about the effects of TMS, are limited by technical problems related to finding an appropriate coil size for small animal heads (Weissman et al., 1992; Fitzpatrick and Rothman, 2000). Neural modeling, however, does not suffer from these methodological limitations and thus may be helpful in refining our understanding regarding the neural bases of TMS and its effects on tinnitus. In the past, we (Husain et al., 2002) have investigated the effects of TMS on visual processing and short-term memory system using a large-scale neurobiologically realistic model. Currently, we are testing the effects of rTMS on a neural network model of tinnitus.

Review of tinnitus models

Early neural network modeling of tinnitus was inspired by theoretical models that described possible neural mechanisms mediating tinnitus (Møller, 1984, 1995; Jastreboff, 1990). Møller (1995) described a central auditory process wherein reduced spontaneous activity due to deafness causes a decrease in local inhibition, which in turn causes increased excitation, boosting neural activity and leading to tinnitus. Jastreboff (1990) regarded tinnitus to be a phantom sensation and proposed that tinnitus is a result of high levels of neuronal activity caused by the general increase in

the responsiveness of central auditory neurons and involves a network of peripheral and central auditory processing regions.

The majority of the neural models of tinnitus have utilized a lateral-inhibition network (LIN) (Gerken, 1996; Kral and Majernik, 1996; Bruce et al., 2003; Dominguez et al., 2006). One such LIN is depicted in Fig. 1. In an LIN, a neuronal element inhibits its neighboring elements within the same layer via inhibitory connections. Such lateral inhibition is the defining feature of an LIN. The word layer in this context refers to levels or tiers of neuronal elements; it need not refer to one of the six cortical layers. It may receive (excitatory) input from the layer (or module) one level below it and transmits this activity to the next module or to the next level. The popularity of an LIN type of model to simulate tinnitus is perhaps not

surprising. LINs have been shown to exist throughout the central auditory processing system and in multiple species (Houtgast, 1972; Shamma, 1985; Ehret and Merzenich, 1988; Suga, 1995). The fundamental assumption made by the models is that a certain perturbation of the LINs in the central auditory system due to sensorineural hearing loss leads to tinnitus (it should be noted however, that not every individual with hearing loss has tinnitus). Reduced inhibition in the central auditory structures (Szczepaniak and Møller, 1996; Abbott et al., 1999; Milbrandt et al., 2000) can lead to hyperexcitability (Salvi et al., 1990, 2000), which in turn may lead to tinnitus generation. The models differ from each other in the putative location of the LIN and the degree of realism incorporated into the neuronal elements comprising the LIN.

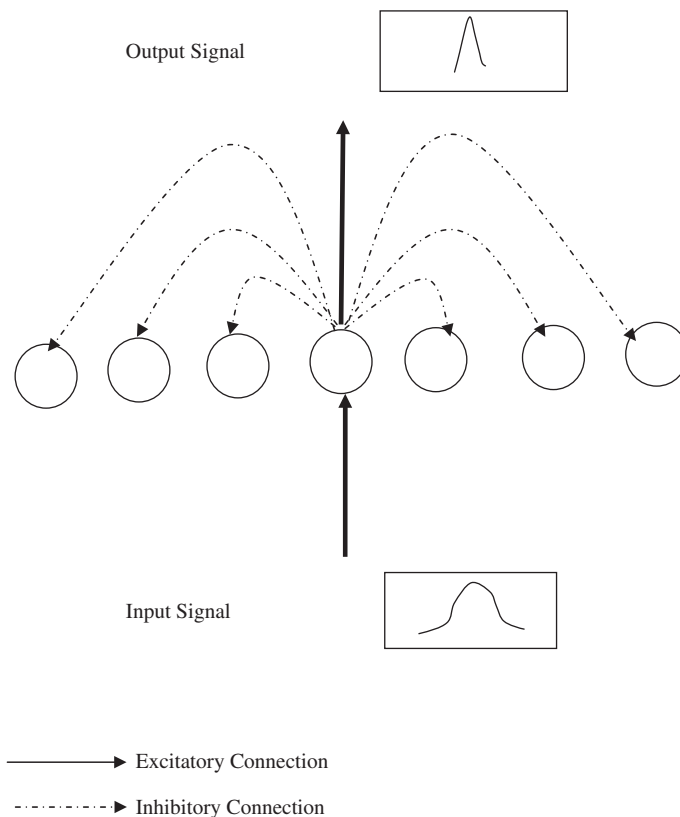


Fig. 1. Representation of the architecture of a lateral-inhibition network (LIN). The sharpening of the input due to the LIN is depicted using simplified representations of input and output signals.

In the [Kral and Majernik \(1996\)](#) model, the location of the LINs is not explicitly stated; such LINs may occur anywhere in the processing stream from the cochlea to the cortex, or multiple LINs may span several regions. A single layer (or module) of the LIN model ([Kral and Majernik, 1996](#)) consists of 1000 processing elements that are connected to their counterparts in the next layer via a weighted excitatory connection and to the counterpart's neighbors via weighted inhibitory connections. It should be noted that the neuronal elements only connect to the elements of the next layer. The traditional instantiation of an LIN involves inhibition of the neighboring elements within the same layer (e.g., [Gerken, 1996](#); [Bruce et al., 2003](#)). A linear threshold function governs each element's activity and sharpens the representation of the input, enhancing the contrast within it.

Spontaneous activity of an auditory nerve fiber (or "neural noise") can be modeled as a Poisson-like process, which has an uneven probability density function of interspike intervals. The LIN processes this activity in a non-linear fashion, enhancing certain parts and dampening others. During normal processing, the neural noise is masked by the stimulus or by the ambient wide-band acoustic noise. However, for individuals with hearing loss, such masking does not exist for a part of the hearing spectrum, and therefore the spontaneously generated neural noise is not masked, resulting in the sensation of tinnitus: the LIN amplifies abrupt transitions in the input ("the edge effect") caused by notch-like sensorineural hearing loss (modeled as a gap in a noisy signal). [Kral and Majernik \(1996\)](#) hypothesize that the processing of the neural noise by an LIN-like system in the presence of hearing loss can lead to tinnitus.

[Gerken's \(1996\)](#) model utilizes an LIN that is located in the inferior colliculus. Gerken cites several reasons, all of which have support from the available literature, to locate the tinnitus-generating system within the inferior colliculus: the distribution of lateral inhibition in the inferior colliculus nucleus, possible changes in inhibition following hearing loss, and the merging of auditory and non-auditory functions, specifically, the initiation of aversive behavioral responses, within

the inferior colliculus. A central assumption of Gerken's model, as in the Kral and Majernik model, is that the unevenness in the spontaneous neural activity of the cochlea is exaggerated by central mechanisms of lateral inhibition. The input to the model, in the absence of acoustic input, is the spontaneous activity of the peripheral levels of the auditory system. A cochlear injury, resulting in hearing loss or deafness, reduces the firing rate in auditory nerve fibers for those fibers that represent the parts of the frequency range where the hearing threshold is elevated.

[Bruce et al. \(2003\)](#) made the LINs more neurobiologically realistic by adding temporal behavior of real neurons to the model's neuronal elements. They employed leaky integrate-and-fire neuronal models that incorporate both passive temporal dynamics and active spiking and refractory behavior. Their recurrent LIN, as in other LIN models, enhanced the edges and peaks of the input. The main prediction of this model, as with the [Gerken \(1996\)](#) and [Kral and Majernik \(1996\)](#) models, is that the enhancement of the edge between the normal and reduced spontaneous activity (due to hearing loss) results in an output similar to that elicited by a tonal stimuli. It was a novel finding in this study that the degree of edge enhancement was dependent on the mean input and output spike rates in the normal region of spontaneous activity, which meant that it was governed by the amount of inhibitory interactions between neighboring neurons. These predictions are testable by experiments.

The [Dominguez et al. \(2006\)](#) model of tinnitus is an extended version of the [Bruce et al. \(2003\)](#) model, with the latter model, which simulates the auditory brain-stem response, providing the input to the cortex-based Dominguez model. The Dominguez LIN model uses integrate-and-fire spiking neurons that form an input layer representing thalamic neurons and an output layer representing the primary auditory cortex. In order to investigate the generation of tinnitus, [Dominguez et al. \(2006\)](#) considered three model architectures under five simulation conditions. The architectures were: a "normal" model with normal inputs from the thalamic layer; an "impaired" model which receives input from a damaged cochlea, but has

no other differences from the normal model; and a “compensated impaired” model, which receives input from the damaged cochlea and in addition, has compensatory changes in the lateral connection strengths in the cortical model.

The three architectures were tested under five conditions — presentation of only the spontaneous input, and of four different input tones, one in the normal hearing region, one to either side of the edge of hearing loss, and one in the impaired region. The normal model treated all the frequencies in the spontaneous input in the same manner. The impaired model showed decreased activity for the frequencies in the region of the hearing loss; in contrast, the compensated impaired model showed increased activity in the region of hearing loss, consistent with experimental evidence (Eggermont, 2003; Seki and Eggermont, 2003). Among the three models, the compensated impaired model behaved most like a tinnitus model in its response to tones within and at the edges of the impaired region because it showed stimulus-driven response in these regions, which the impaired model did not. The compensated impaired model also exhibited increased activity at the edge of the hearing loss, in a manner that is assumed to be involved in causing hyperacusis that occurs frequently in individuals with tinnitus. The authors suggest that the change in the balance of excitation and inhibition in the lateral (within the same layer) connections, implemented in the compensated impaired model, resulted in the simulation of the generation of tinnitus in the model. The simulated tinnitus was characterized by elevated spontaneous activity in the affected deafferented region, hyperexcitability at the edge of the hearing loss, an increase in synchrony in spontaneous firing, and some spread of activation in the impaired region when driven by a tone at the edge of hearing loss.

Of the models reviewed here, the Dominguez model provides the most comprehensive simulation of tinnitus generation as it is known from physiological studies. However, as with the other models there is no attempt to distinguish neural plasticity due to hearing loss from that due to (or causing) tinnitus. Tinnitus is not an automatic consequence of sensorineural hearing loss; as many as 60% of the people with some form of

hearing loss do not develop tinnitus (Lockwood et al., 2002).

A major prediction of the Dominguez model (as of all other LIN models) is that the edge-effect (amplification of sounds with frequencies near the edge of the hearing loss) leads to spurious or phantom perception of non-existent sounds. Tinnitus can resemble many different kinds of sounds, bells, whistles, or broadband noises; it can be of varying nature and can have varying pitch, and occur not only at the edge of the hearing loss but throughout the hearing loss region (Eggermont, 2003). Another weakness of the reviewed models is that they implicitly or explicitly assume that the spontaneous activity in the impaired cochlea, processed through the central auditory system, leads to tinnitus. But this is not necessarily true because complete deafferentation of the auditory nerve (abolishing input from the cochlea) can also result in tinnitus (House and Brackman, 1981; Matthies and Samii, 1997).

Other weaknesses of the reviewed models relate to the assessment of the occurrence of tinnitus in the model and the focus on unitary regions as sources of tinnitus. These are discussed in detail below.

Challenges of modeling tinnitus

The primary challenge of neural modeling of subjective tinnitus is the same one faced by animal models of tinnitus — how do we know that the model (or animal) has tinnitus? Studies using animal models of tinnitus (Jastreboff and Sasaki, 1994; Bauer et al., 1999), (see Chapters 9, 10, 12 and 13) have addressed this problem in one of the two ways — either by using behavioral measures or neuronal activity measures that are indicative of the animal having tinnitus. In animal studies, where tinnitus is induced either pharmacologically or by noise-induced trauma, abnormal activity has been observed in the periphery and the central auditory processing structures (Eggermont, 2005). Whereas the neuronal activity in the auditory nerve fibers generally decreased or remained the same (Liberman and Kiang, 1978; Muller et al., 2003), the spontaneous neuronal activity in the

central auditory system has typically increased in response to trauma. These increases have been reported in the inferior colliculus and other brain stem nuclei (Chen and Jastreboff, 1995; Manabe et al., 1997; Wallhauser-Franke and Langner, 1999; Kaltenbach et al., 2000), in the primary auditory cortex (Norena and Eggermont, 2003; Seki and Eggermont, 2003) and in the secondary auditory cortex (Eggermont and Kenmochi, 1998) (see also Chapters 2 and 6). The reviewed models rely on qualitative matching with electrophysiological animal data to infer the simulation of tinnitus. Thus, if simulated hearing loss in a model results in changed spontaneous activity in its modules, one may take this to be an indication of tinnitus. In a manner similar to the animal studies, one can make the assumption that a model has tinnitus if it has increased spontaneous activity in a component of the model and if it is poorer in discriminating sounds near its “tinnitus” sound. However, this assumption does not discriminate between changes in spontaneous activity due to hearing loss alone and that due to a combination of hearing loss and tinnitus.

A better solution for the evaluation of tinnitus may be to make the assumption that the poorer performance of partially deafened animals in discriminating certain sounds, as compared to controls, is indicative of the animal having tinnitus. In studies using animal models (Jastreboff et al., 1988; Bauer et al., 1999; Heffner and Harrington, 2002; Guitton et al., 2003; Ruttiger et al., 2003), animals are usually trained to respond to the absence of an acoustic stimulus prior to deafening. In some studies, the presence of tinnitus (post deafening) is ascertained by the errors made by the animal in “silent” trials, indicating that the animals heard something in the absence of an acoustic stimulus. These studies require elaborate training and behavioral paradigms that can be difficult to implement. A recent study (Turner et al., 2006) uses the acoustic startle reflex for rapid tinnitus screening in rats (Chapter 13).

There exists a third possibility of validating a model with tinnitus which is unique to neural models: a quantitative match between the simulated brain imaging data from a tinnitus model and experimental brain imaging data from human

subjects with tinnitus. Functional MRI (and other neuroimaging tools) can provide objective measures of the relation between neural activity and tinnitus and allow for the identification of tinnitus-related activity at a neural level (Melcher et al., 2000). Correlating tinnitus with neural activity in humans provides a way to validate models of tinnitus.

Another challenge of modeling tinnitus is to identify which parts of the auditory system are included in the model. Historically, the areas included in a tinnitus model have reflected the state of our understanding regarding tinnitus origins. Models of tinnitus have simulated data in single modules representing cochlea and electrical activity in the auditory nerve (Kral and Majernik, 1996; Yi et al., 2001a, b), the inferior colliculus (Gerken, 1996), parts of the central auditory processing system (Bruce et al., 2003), and recently, the thalamus and the primary auditory cortex (Dominguez et al., 2006). However, results of the latest research on tinnitus using human subjects and PET/fMRI techniques indicate that *several* brain regions are implicated in tinnitus generation and modulation (Lockwood et al., 1998, 2001, 2002; Giraud et al., 1999; Mirz et al., 2000a, b). The results suggest that tinnitus is influenced by (and in turn affects) a network of regions, including somatosensory (Chapter 10), limbic (Chapters 1 and 3), and motor regions (Bauer, 2004). This in turn implies the need of a large-scale neural model to adequately address the multiple brain regions involved in tinnitus. Large-scale models that incorporate multiple regions allowing for the simulation of tinnitus as an emergent property and the representation of the complex ways in which somatosensory, limbic, and motor influences affect tinnitus, will greatly advance our knowledge of the pathophysiology of tinnitus.

In the next section, we describe a large-scale neural network model of auditory object processing, which can potentially be used to simulate tinnitus. The model has the added advantage that it can simultaneously simulate electrical, behavioral, and neuroimaging data thus allowing for comparison with multiple sources of tinnitus data.

Proposed neural network model of tinnitus

Because tinnitus is an auditory disorder, frequently developing after sensorineural hearing loss, a reasonable course is to start with a model of normal auditory processing and perturb it in a systematic manner to induce tinnitus. For this reason, we plan to use a previously developed, large-scale, neurobiologically realistic model of auditory processing to investigate the neural bases of tinnitus. The model (Husain et al., 2004) was constructed based on neurophysiological and neuroanatomical data from primate and human studies and incorporates modules representing regions ranging from primary auditory cortex, through secondary and tertiary auditory processing areas in the temporal cortex, to the prefrontal cortex (PFC) (see Fig. 2). Each module of the

network is composed of 81 basic units. The model processes auditory objects such as frequency-modulated (FM) sweeps in a delayed-match-to-sample (DMS) short-term memory task. A DMS task consists of the presentation of a stimulus, a delay, and a second stimulus followed by a response period. The input to the model is via the medial geniculate body (MGB), each unit of which represents a neuronal population selective for a particular range of frequencies. The first two stages of the model, Ai (primary auditory cortex) and Aii (secondary auditory cortex), perform feature detection: FM sweep-selective neuronal subpopulations in Ai and Aii respond to the presence of upward and downward sweeps in the input signal. The units of Aii have a longer spectrotemporal window of integration than the Ai units; therefore they are selective to longer duration FM

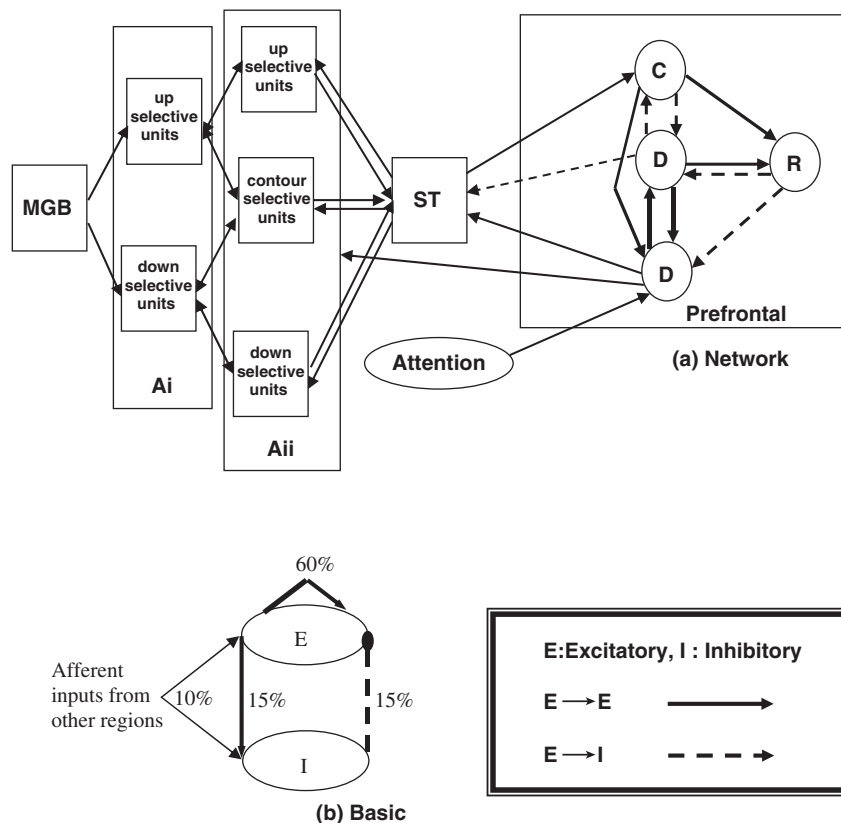


Fig. 2. (a) Network diagram of the large-scale auditory object processing model (Husain et al., 2004). (b) Basic unit. Each individual module in the network is composed of 81 basic units, each of which is composed of an excitatory and an inhibitory element.

sweeps. In addition, Aii has a third type of unit — the “contour-selective” element. The contour-selective units respond to changes in sweep direction that occur in relatively brief periods of time. The ST (superior temporal sulcul/gyral area) module receives inputs from all three subpopulations of Aii and integrates the features into an abstract distributed representation, or a “percept.” The percept is then forwarded onto the short-term working memory system of the PFC. There are four types of units in the PFC: cue-sensitive units that respond to the presence of an input; two types of delay units, D1 and D2, that maintain a stable representation of the percept of the first stimulus of a DMS trial and facilitate its comparison with that of the second stimulus; and Response module units that are active to a greater extent when the second stimulus is a match than when it is not a match. The delay unit D1 is active during the delay period between the presentations of the stimuli whereas delay unit D2 is active during both the delay and the subsequent stimulus presentation. A match trial (the model judges the pair of stimuli in a DMS task to be similar) is indicated by a greater (above a threshold) number of active response units, a non-match trial by fewer active response units.

The basic unit underlying all the regions of the model consists of excitatory and inhibitory elements, with the excitatory element contributing more to the overall activation of the basic unit due to its larger synaptic weights. Such a unit is commonly used in modeling studies and was first introduced by [Wilson and Cowan \(1972\)](#). The activities of the excitatory and inhibitory elements of each basic unit (ranging in value from 0 to 1) are governed by a sigmoidal activation rule whose parameters represent different aspects of cortical dynamics — for instance, internal noise, threshold, rate of increase in the presence of the stimulus, decay at the offset of the stimulus, etc. The basic unit can be thought of as representing a simplified cortical column with the excitatory element corresponding to the pyramidal neuronal population, and the inhibitory element corresponding to the population of inhibitory interneurons.

We ([Husain et al., 2004](#)) validated the large-scale auditory model using the results from an

fMRI experiment employing stimuli and tasks similar to those used in our simulations. The task performed was the DMS task employing FM sweeps and pure tones. The hemodynamic PET/fMRI data were simulated by integrating the absolute value of the synaptic activities over the time course of the study within the different regions for each task. We assumed that increases in either excitatory or inhibitory synaptic activity, or both, are manifest as increased PET/fMRI activity ([Jueptner and Weiller, 1995](#); [Logothetis et al., 2001](#)). Our results demonstrated that the model is capable of exhibiting the salient features of both electrophysiological neuronal activities and fMRI values that are in agreement with empirical data.

Several researchers ([Jastreboff, 1990](#); [Lockwood et al., 2002](#); [Eggermont, 2005](#)) have noted that the phantom or illusory nature of tinnitus is similar to the phantom-limb sensation. The large-scale auditory model has been successfully used to investigate an illusory auditory percept, specifically, the continuity illusion ([Husain et al., 2005](#)); this lends further support for using the model to investigate the illusory nature of tinnitus. The auditory continuity illusion refers to a perceptual grouping phenomenon in which a sound is perceived to continue through occluding noise even though no signal is physically present in the noise. It serves the ecological purpose of making communication sounds intelligible in a noisy environment. In order to investigate the neural bases of the continuity illusion, we simulated different stimuli: original intact stimuli composed of FM sweeps; gapped stimuli with silent gaps inserted into the original stimuli; and gapped stimuli with noise inserted in the gaps. The model perceived stimuli with small gaps to be as continuous as the original stimuli, but this was not the case for stimuli with larger gaps. When broadband noise was inserted into the larger gaps, the stimuli were perceived as continuous by the model. This behavior of the model is similar to the reported behavior of humans and animals ([Dannenbring, 1976](#); [Sugita, 1997](#)) in perceiving the illusory continuity of sounds. The model was unchanged from its original formulation for the continuity illusion investigation, thus attesting to the robustness of the model.

The predominant mechanism mediating this illusion is the divergence of the feedforward connections in the first three feature processing modules (Ai, Aii, and ST) located in the temporal cortex.

We plan to use a modeling-experimental framework that will allow us to elucidate the significance and consequence of individual tinnitus-related factors by combining the model with suitably designed fMRI experiments. The primary advantage of the proposed model compared to the other tinnitus models is that it can simultaneously simulate electrophysiological, behavioral, and fMRI data, allowing for comparisons with both human and animal studies of tinnitus. In a manner similar to the work of [Edin et al. \(2007\)](#), we propose to distinguish between different neural mechanisms subserving tinnitus. Presence of tinnitus will be measured as a combination of (1) increased spontaneous neural activity in the three temporal cortex modules, Ai, Aii, and ST, when no external stimulus is present, (2) decreased performance in discrimination of certain sounds, and (3) strong agreement with experimental fMRI data. One method of inducing tinnitus is to alter the input coming into the Ai via MGB. The altered input is noisier reflecting the changes in the MGB (thalamus) caused by hearing loss. The noisier input will result in lowered threshold and/or increased noise at Ai. Both threshold and noise are parameters of the basic units' sigmoidal equation. A second mechanism is to alter the excitation-inhibition ratio of each modeled cortical column, by increasing the weights of the self excitatory-to-excitatory connections. A third mechanism is to alter the attention feedback to the auditory cortex in order to determine the effects of top-down factors in tinnitus perception. The attentional subsystem (see [Fig. 1](#)) in the model is a composite of top-down processes that affect the model's performance in a given simulation, in this case, during tinnitus. Tinnitus is concomitant with an altered tonotopic map in the auditory cortex ([Mühlnickel et al., 1998](#)). A fourth method of simulating tinnitus is to alter the topological connections in the Ai module of the model. Note that these perturbations can occur throughout the module or for a smaller subsection of the module, mimicking partial hearing loss. By systematically varying each of these

model parameters and matching against experimental fMRI data from volunteers with and without tinnitus, we plan to identify the likeliest neural mechanisms of tinnitus.

To illustrate this approach, we describe our preliminary results from changes to one of the model parameters, specifically, the noise parameter of Ai units. The noise parameter reflects the internal, random, spontaneous noise in the system. As shown in [Fig. 3a](#), increasing the noise resulted in increased integrated synaptic activity (precursor of PET/fMRI activity) predominantly in Ai and to a smaller extent in Aii, ST, and PFC, compared to the simulations with the baseline noise parameter value. There was also increased electrical activity in these regions following the same pattern (not shown). These results agree with the reported findings of increased neural activity in the primary auditory cortex ([Seki and Eggermont, 2003](#)) and also increased PET/fMRI activity in the auditory cortices ([Andersson et al., 2000](#); [Mirz et al., 2000b](#); [Lockwood et al., 2001, 2002](#)). Increasing the noise parameter value also disrupted the behavior of the model as shown in [Fig. 3b](#). In order to test the behavior of the model, we simulated both matching and non-matching DMS trials. In the baseline simulations, there were 11 Response module units active for a match trial and 5 Response module units active for a non-match trial. In the perturbed model, there was reduced activation for both match and non-match trials: 10 units were active for the match trial and 2 for the non-match trial. Although these simulations were done by varying only one parameter, they suggest that it is possible to induce tinnitus-related activity in the model. Detailed simulations are being conducted to investigate the effects of other model parameters, in isolation or in combination, in inducing tinnitus. We are also in the process of dissociating the effects of hearing loss alone from that of hearing loss combined with tinnitus within the model.

A large-scale neural network allows us to investigate the modulatory effect of other regions on the auditory processing areas implicated in tinnitus generation. In a separate series of simulations, we propose to study the modulatory effect of other regions, not presently included in the model, on tinnitus generation. Two limbic structures

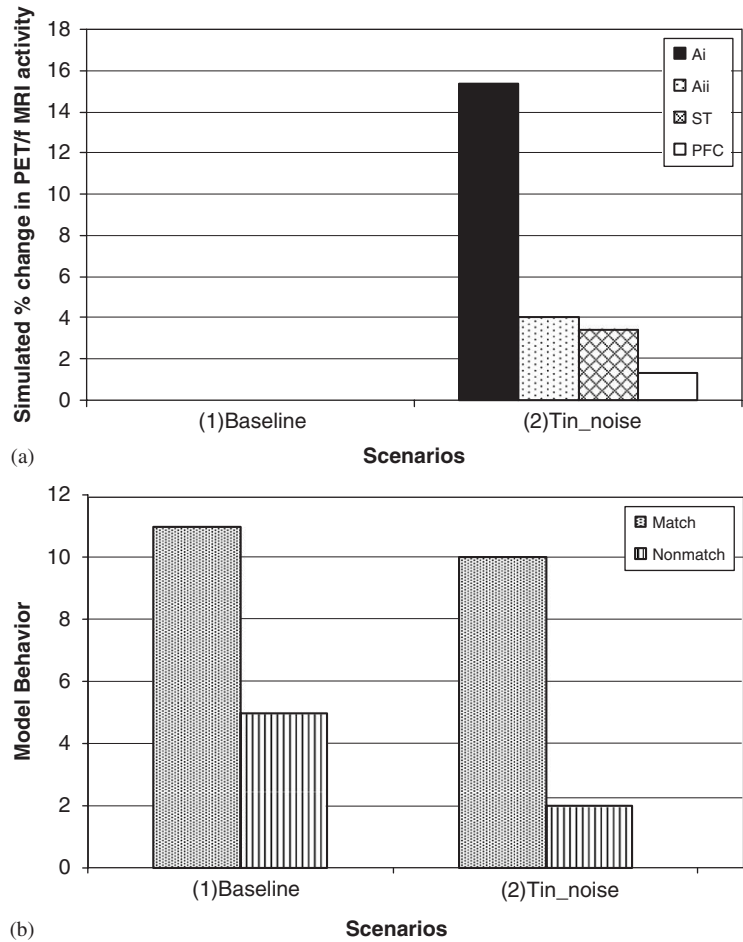


Fig. 3. (a) Percent signal change in simulated PET/fMRI values for the tinnitus scenario compared to baseline (normal operation of the model) in the 4 regions of the model. Scenario 1 is the baseline; all its values are at 0% change. We increased noise parameter of the basic units of Ai from a baseline value of 0.05 to 0.25 to simulate tinnitus. The activation values of the basic units range from 0 to 1. (b) Simulated behavior of the model in normal and tinnitus scenarios.

associated with emotion processing have been implicated in modulating tinnitus: the amygdala and the nucleus accumbens, part of the paralimbic ventral striatum. Animal studies have shown that the metabolism of the amygdala increases after administration of salicylate as does that of the MGB of the thalamus and the auditory cortex (Wallhauser-Franke et al., 1996; Zhang et al., 2003). A structural imaging study (Muhlau et al., 2006) has shown significant gray matter decreases in the ventral striatum region combined with gray matter increases in the medial geniculate nucleus of the thalamus. Muhlau et al. suggest that

because of the interconnected parallel circuits between the nucleus accumbens and the thalamus, the nucleus accumbens can exert an inhibitory gating effect on the thalamocortical relay. The dorsal-lateral parts of the MGB also projects to the amygdala (see Chapter 3). An fMRI study (Lockwood et al., 1998) has also provided evidence of aberrant connections between the limbic (specifically, the hippocampus) and auditory processing systems. Addition of limbic regions to the model may allow us to answer an outstanding question regarding tinnitus — why certain persons, but not all, with hearing loss develop tinnitus

(Lockwood et al., 2002). In this scenario tinnitus is not a mechanistic development resulting from some form of hearing loss, but instead it is modulated by the emotional processing regions of the brain.

Conclusion

In this chapter, we discussed the usefulness of applying the technique of neural network modeling to investigate the neural bases of tinnitus. A model can account for diverse sets of data within a common framework and make testable predictions that in turn can lead to the designing of experiments to test these predictions. Of the several models of tinnitus, a majority has relied on the LIN to simulate tinnitus and focused on the central auditory processing regions as possible anatomical locations of the physiologic abnormalities that cause tinnitus. Recently, studies using neuroimaging tools have identified other brain regions that may be involved in mediating or modulating tinnitus or are affected by it. We described some challenges faced by models of tinnitus, one of which is the assessment of the occurrence of tinnitus in the model. The neuroimaging measures obtained from human studies provide a possible objective way to evaluate a subjective phenomenon such as tinnitus. We propose a new large-scale neurobiologically realistic model of tinnitus, whose simulated data can be compared against experimental electrophysiological, behavioral, and neuroimaging data to evaluate the simulation of tinnitus. A combined modeling-experimental framework allows us to identify not only the brain regions involved in tinnitus but also evaluate the feasibility of different neural mechanisms mediating tinnitus.

Abbreviations

DMS	delayed-match-to-sample
EEG	electroencephalography
FM	frequency-modulated
fMRI	functional magnetic resonance imaging
LIN	lateral-inhibition network

MEG	magnetoencephalography
MGB	medial geniculate body
PET	positron emission tomography
PFC	prefrontal cortex
rTMS	repetitive transcranial magnetic stimulation

Acknowledgments

The author thanks Barry Horwitz, Jason Smith, and Nathan Pajor for reading versions of this chapter and for fruitful discussions. The author's work was supported by the NIDCD-NIH Intramural Program and a grant from the Tinnitus Research Consortium.

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CHAPTER 12

Salicylate-induced tinnitus: molecular mechanisms and modulation by anxiety

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Abstract: Tinnitus is a pathology, which severely impairs the quality of life, and for which no efficient therapy exists. One reason is the lack for clear understanding of the molecular mechanisms of this pathology. For example, the anatomical site and the molecular pathways responsible for the generation of tinnitus are still under debate. This is due, in part, to the difficulty to induce and measure tinnitus in animals. This paper summarizes the recent discoveries provided by the use of salicylate as a model of tinnitus. The first is the demonstration that salicylate acts at the periphery by activating on cochlear NMDA receptors that are not “normally” implicated in the transmission of auditory message to the brain. The second discovery is the clear demonstration that strong relationships exist between anxiety and perception of tinnitus. Interestingly, application of NMDA antagonists onto the round window membrane abolished tinnitus, even in animals receiving a treatment with the anxiogenic serotonergic agent meta-chlorophenylpiperazine (mCPP). In addition to classical psychotherapeutic treatments, targeting cochlear NMDA receptors, by local infusion of drugs into the middle ear to reach the cochlea, may represent a promising therapeutic strategy to cure incapacitating tinnitus, even in depressed or chronically anxious patients.

Keywords: tinnitus; cochlea; NMDA receptor; salicylate; anxiety; local therapy

Introduction

Constantly perceiving a sound, without any way to make it cease, implies a state which can be highly anxiogenic, and which may severely impair the quality of life (Coles, 1983; Dieroff and Meissner, 1987; Nicolas-Puel et al., 2002; Guitton, 2006). Despite tinnitus is a severe disorder, there is no efficient treatment is known. Biological

mechanisms that cause tinnitus are still mostly unknown. One of the reasons lies undoubtedly in the difficulties in developing relevant animal models of tinnitus, which can be regarded as pathology of perception. Progress in understanding of the pathophysiology of tinnitus and finding effective treatments depend on the availability of relevant animal models (Eggermont, 2005; Guitton, 2006). Animal models have already contributed to our knowledge of tinnitus. This is particularly true for the model of tinnitus induced by salicylate (Jastreboff et al., 1988; Jastreboff and Sasaki,

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1994; Bauer et al., 1999). The purpose of the present chapter is to discuss the contribution of the model of tinnitus that is based on salicylate-induced tinnitus.

Advantages of salicylate-induced tinnitus as a model

Salicylate, the active component of aspirin (acetylsalicylic acid), is a vegetal compound first extracted from bark of willow tree. Salicylate is a well-known nonsteroidal anti-inflammatory agent (Vane, 1971). More than a century ago, at an early stage of its clinical use, salicylate was found to cause hearing loss and tinnitus in humans (Sée, 1877). Later on, large doses of salicylate have been shown to induce tinnitus in animals (Jastreboff et al., 1988), and were then extensively used in animal studies of tinnitus (Cazals et al., 1998; Bauer et al., 1999; Cazals, 2000; Guitton et al., 2003, 2005). Salicylate-induced tinnitus is characterized both in humans and animals by their replicability and reversibility. Due to the high reliability of tinnitus induced by salicylate, this molecule has therefore been considered as a very powerful and useful tool to experimentally induce tinnitus in animals, thus providing a calibrated way to analyze some of the basis of tinnitus (Jastreboff et al., 1988; Bauer et al., 1999; Guitton et al., 2003). Salicylate thus represented during several decades the privileged way to induce tinnitus in the context of biomedical research (Jastreboff and Sasaki, 1994). While hearing loss induced by salicylate is due to the competition of this molecule with cytoplasm chloride's contribution to nonlinear capacitance of outer hair cells (Kakehata and Santos-Sacchi, 1996; Oliver et al., 2001), the details of the mechanisms of salicylate-induced tinnitus were only recently elucidated (Guitton et al., 2003; Peng et al., 2003; Guitton and Puel, 2004).

The salicylate model of tinnitus has recently contributed two important pieces of information to our understanding of tinnitus. The first was the discovery that the change in synaptic transmission in the cochlea brought about by salicylate is one of the key factors in the generation of tinnitus (Guitton et al., 2003, 2004; Peng et al., 2003).

Following this discovery, strong relationships between emotions and perception of tinnitus has been evidenced at the central level (Guitton et al., 2005). The understanding of the importance of these two factors may promote the development of preclinical and clinical treatment. The present chapter reviews some of the knowledge obtained using the model of salicylate-induced tinnitus and further discusses the involvement of anxiety in the perception of tinnitus.

Peripheral tinnitus: pathology of the cochlear sensory cell synapse

Developing — and more important, optimizing — an efficient therapy for tinnitus requires identification of correct targets (i.e., appropriate anatomical locations, and specific molecular pathways) involved in the generation of tinnitus (Eggermont, 2005; Guitton, 2006). Further works are required to directly apply results obtained from animal models of tinnitus induced by salicylate to other types of tinnitus such as noise-induced tinnitus, and age-related tinnitus. However, studies performed on such animal models have contributed much to our understanding of the molecular and cellular mechanisms of the generation of tinnitus. The fact that the anatomical site of generation, and the molecular pathway involved in the generation of salicylate-induced tinnitus have been identified has contributed to understanding of the pathophysiology of tinnitus (Guitton et al., 2003; Guitton and Puel, 2004).

Identification of the anatomical localization of tinnitus “generator” (i.e., identification of molecular and anatomical targets) is important for the development of therapeutic tools. Results from early studies of the animal model of salicylate-induced tinnitus provided important insights regarding the anatomical location of the physiological abnormalities that caused the tinnitus. Electrophysiological studies showed that administration of salicylate cause increase of the spontaneous activity of single units of the auditory nerve (Evans and Borerwe, 1982; Stypulkowski, 1990). These results were interpreted as an indication that the anatomic substrates of salicylate-induced tinnitus

were located at the periphery of the auditory pathway.

Later studies of the spontaneous neural noise that can be recorded from the round window in the absence of sound stimulation and which corresponds to the ensemble measure of the auditory nerve spontaneous firings of recordings in silent conditions (Schreiner and Snyder, 1987; Dolan et al., 1990; Cazals et al., 1998) had a spectral peak at 900 Hz. The recorded neural noise is related to the diphasic spontaneous discharge of individual auditory nerve fibers (Dolan et al., 1990). It has been shown that the spectral 900 Hz peak is closely related to the cochlear sensitivity. It is only present in healthy cochlea with normal hearing threshold (Dolan et al., 1990; Cazals et al., 1998; Searchfield et al., 2004). In contrast, a narrow spectral peak at 250 Hz has been reported in animal models of tinnitus (Schreiner and Snyder, 1987; Cazals et al., 1998) and in patients experiencing tinnitus (Martin et al., 1993). Modifications of the spectrum of the neural noise were correlated with the occurrence, the development, and the reversibility of salicylate-induced tinnitus in animals (Cazals et al., 1998). These results supported the assumption that salicylate-induced tinnitus resulted from a dysfunction of peripheral structures (i.e., inside the cochlea or the auditory nerve).

A new paradigm was recently added to the behavioral protocols rats aiming to allow a quantification of tinnitus induced by salicylate (300 mg/kg/day for 4 days). This paradigm, which is based on an active avoidance paradigm, proved itself to be very efficient in the context of salicylate-induced tinnitus (Guitton et al., 2003, 2005). Briefly, the behavioral indicator of the occurrence of tinnitus was determined by counting the number of false positive responses observed after the animals had been conditioned to respond to hearing a sound by displaying a motor task (Guitton et al., 2003). Animals were trained to jump on a climbing pole upon hearing a sound — the false positive responses being the number of climbs observed during silent periods (Fig. 1). In contrast to other protocols in which animals are deprived of food or water — in some case leading to major loss of body weight (Jastreboff et al., 1988; Jastreboff and Sasaki, 1994; Bauer et al., 1999), this

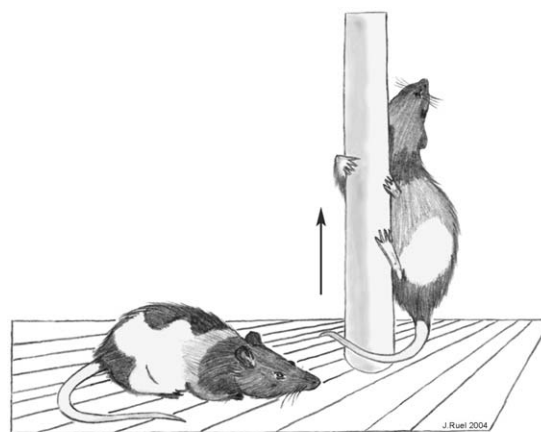


Fig. 1. Behavioral paradigm to assess the occurrence of tinnitus in rats: animals were conditioned to perform a motor task (in this case, to jump to a climbing pole) when a 10 kHz tone is presented. When they are treated with salicylate, animals execute the motor task during the silent periods. They behave as if they hear a sound when no external sound is presented, because they experience tinnitus (Courtesy J. Ruel).

paradigm did not involve changes in the animals' physiological states. This presented great advantages, especially when surgical procedures are required in order to apply drugs locally (i.e., directly in the contact of cochlear fluids through the round window membrane) to the question of the site of generation of tinnitus induced by salicylate.

Based on the fact that inner hair cells use glutamate as neurotransmitter to convey the auditory information to the brain, glutamate antagonists were used to block salicylate-induced tinnitus. While the normal synaptic transmission between inner ear cells and primary auditory neurons is mediated by AMPA receptor (Glowatzki and Fuchs, 2002), cochlear cells also express NMDA receptor subunits. Noteworthy is that these NMDA receptors do not seem to be involved in cochlear synaptic transmission. However, some studies have shown that they are implicated in synaptic repair after excitotoxicity (d'Aldin et al., 1997). Furthermore, NMDA antagonists prevent excitotoxicity induced by cochlear ischemia and acoustic trauma (Puel et al., 1994; Duan et al., 2000). Since NMDA receptors seemed implicated in pathological conditions known to induce tinnitus — or at least

linked to tinnitus — NMDA antagonists were thus thought to possibly constitute attractive candidates for the treatment of tinnitus (Guitton et al., 2003, 2005). Indeed, local application of three different NMDA antagonists: 7-chlorokynurenate (glycine-site antagonist), gacyclidine (PCP-site antagonist), and the channel blocker MK-801 (Guitton et al., 2003, 2004) blocked tinnitus induced in animals by salicylate treatment. It is noteworthy that these antagonists had their effect in very low concentrations, especially given the fact that experiments took place *in vivo*, (with a concentration of 50 μ M for 7-chlorokynurenate and gacyclidine, and as low as 10 μ M for MK-801). The finding that tinnitus induced by salicylate is generated in the cochlea through abnormal activation of NMDA receptors contributed to the understanding of the molecular basis of tinnitus. The involvement of these receptors, which are located on peripheral nerve endings that connect to the inner hair cells, is supported by electrophysiological studies performed on primary auditory neurons in cultures showing that salicylate facilitate the response of NMDA receptors (Peng et al., 2003).

A detailed discussion of the molecular links between the augmentation of salicylate concentration inside the cochlea and the activation of NMDA receptors can be found elsewhere (Guitton and Puel, 2004). Briefly, salicylate is known to be a potent cyclooxygenase inhibitor. Thus, salicylate triggers an inhibition of the enzymes that display cyclooxygenase activity. This enzymatic inhibition in turn causes an accumulation of arachidonic acid in the lipid membranes of cochlear cells, which alters the mechanic properties of the membranes, resulting in a stretching of the NMDA receptor and an increase of their probability of opening (Casado and Ascher, 1998; Guitton and Puel, 2004). Complementary experiments performed using mefenamate (another potent inhibitor of cyclooxygenase) in place of salicylate confirmed the involvement of this molecular pathway in the generation of tinnitus by salicylate (Guitton et al., 2003).

Central modulation of peripheral tinnitus

The preceding paragraph discussed the importance of synapses on the hair cells in the cochlea synapses in the generation of tinnitus. However, there is considerable evidence of involvement of the central nervous system in tinnitus; one consequence of that is the weight of anxiety and other factors in the development of tinnitus (Nicolas-Puel et al., 2002; Guitton, 2006).

Anxiety is a complex emotional state (Bourin et al., 1998; Akirav et al., 2006), which is also a well-known companion of tinnitus (Schneider et al., 1994; Guitton, 2006). Indeed, the overall severity of tinnitus is known to be related to the anxiety it causes (Halford and Anderson, 1991). However, the question whether anxiety creates tinnitus or whether anxiety exacerbates pre-existing tinnitus still remains to be elucidated. This issue was thus approached by determining the contribution of anxiety in the perception of tinnitus in animals with salicylate-induced tinnitus.

From a molecular point of view, many neurotransmitter systems have been shown to be involved in the establishment of anxious states, including serotonin, GABA, norepinephrine, acetylcholine, and cholecystokinin (Bourin et al., 1998). However, among them, serotonin has been suggested to play a role of major importance (Lesch et al., 1996; Manji et al., 2001; Gross et al., 2002). Serotonergic agents, such as meta-chlorophenylpiperazine (mCPP), have been used extensively to experimentally induce anxiety in animals (Charney et al., 1987; Singewald et al., 2003; Guitton and Dudai, 2004). mCPP, a 5-HT_{2C} receptor agonist, has been widely used to induce anxiety-like states in animals and anxiety in humans (Bourin et al., 1998). In humans, administration of mCPP has been shown to provoke anxiety both in normal individuals and in individuals suffering from panic attack (Charney et al., 1987; Bourin et al., 1998). Administration of mCPP has also been shown to be a powerful tool to investigate the molecular correlates of anxiety-like states in rats (Singewald et al., 2003; Guitton and Dudai, 2004). The emotional state induced by

mCPP treatment can be considered isomorphic to “state anxiety” in humans (Singewald et al., 2003). Therefore, mCPP was thought to be an appropriate pharmacological tool to induce anxiety in rats with salicylate-induced tinnitus.

In such experiments, tinnitus was evidenced using the aforementioned behavioral paradigm in which the number of false positive responses was used as an indicator of the occurrence of tinnitus. After administration of mCPP treatment, (a single injection of mCPP at 0.1 mg/kg dissolved in saline), the number of false positive responses observed during the recording period was not significantly different from the number of false positive responses in untreated animals (Guillon et al., 2005). Thus, administration of mCPP failed to create detectable tinnitus. A totally different pattern of responses was observed when mCPP was administered together with salicylate. The perception of tinnitus induced by salicylate was then increased nearly twofold. The number of false positive which was of 2.4 ± 0.31 in animals receiving salicylate alone, increased to 4.4 ± 0.37 in animals receiving both salicylate- and mCPP-treatment (Guillon et al., 2005).

The possibility to abolish tinnitus exacerbated by anxiety using the same pharmacological agents, i.e., application of NMDA receptors antagonists in the cochlea may open new possibilities of treating tinnitus. When locally applied into the cochlea, the NMDA antagonist 7-chlorokynureate (at a concentration of $50 \mu\text{M}$) was able not only to block salicylate-induced tinnitus, but also, and more importantly, to abolish the perception of salicylate-induced tinnitus exacerbated by the anxiety and caused by the administration of mCPP (Guillon et al., 2005; Guillon, 2006).

Conclusions and perspective: from animal model to therapeutic strategies

Studies in animal models using salicylate-induced tinnitus have contributed much to our understanding of many aspects on tinnitus. The demonstration that some forms of tinnitus may have a

peripheral origin represented a major step forward. The finding that salicylate induces tinnitus through its action on cochlear NMDA receptors has contributed to understanding how cochlear abnormalities may trigger tinnitus.

The animal model of tinnitus described above has made it possible to study the study of the relationship between anxiety and tinnitus. While anxiety per se does not produce tinnitus, it strongly exacerbates its perception. It was therefore interesting to find that application of NMDA antagonists onto the round window abolished tinnitus, even in the animals where tinnitus was potentiated by anxiety. These findings are likely to promote the development of therapeutic means for tinnitus. In addition to classical psychotherapeutic treatments, targeting cochlear NMDA receptors by local infusion of drugs into the middle ear to reach the cochlea may be a promising therapeutic target for treatment of incapacitating tinnitus, even in depressed or chronically anxious patients. The question whether or not this pharmacological strategy can be extent to others forms of tinnitus is currently being investigated in different kinds of cochlear pathologies such as those caused by noise exposure, administration of ototoxic drugs and from presbycusis.

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CHAPTER 13

Behavioral measures of tinnitus in laboratory animals

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Abstract: The fact that so little is currently known about the pathophysiology of tinnitus is no doubt partly due to the relatively slow development of an animal model. Not until the work of Jastreboff et al. (1988a, b) did tinnitus researchers have at their disposal a method of determining whether their animals experienced tinnitus. Since then, a variety of additional animal models have been developed. Each of these models will be summarized in this chapter. It is becoming increasingly clear that in order to study tinnitus effectively, researchers need some verification that a drug, noise exposure or other manipulation is causing tinnitus in their animals. As this review will highlight, researchers now have a variety of behavioral options available to them.

Keywords: tinnitus; behavior; animal models

Introduction

Tinnitus remains a mysterious and frustrating symptom for millions of people. Tinnitus is equally frustrating for scientists studying it and clinicians trying to treat it. One of the reasons for that is tinnitus has many different forms. The cause(s) of tinnitus remains largely unknown. The underlying pathophysiology of tinnitus remains largely unknown. As a result, effective treatments remain elusive. Real scientific advancements in the field have been slow to develop for this sometimes annoying, sometimes debilitating symptom. There are a variety of reasons that might help explain why so little is known about tinnitus, but one thing is clear, tinnitus simply has not been studied adequately. A National Library of Medicine PubMed literature search bears this observation

out. Plotting the number of “hits” using the search term “tinnitus” and several other sensory maladies as a function of time shows that while research on many other diseases has increased greatly over the last 50 years, research on tinnitus has remained at a low level (Fig. 1). With the relatively low level of research on tinnitus, it should not be surprising that so little is known. Tinnitus is due for a surge in research.

One of the reasons for the lack of research and understanding on tinnitus is that it has been historically difficult to objectively measure. Hearing scientists are used to measuring responses to acoustic stimuli but are unprepared for how to measure responses to stimuli that are not actually there. This is the crux of the problem for subjective tinnitus, which is generally defined as an internal sound representation without an external physical source. The internal nature of the symptom makes the study of human tinnitus a matter of asking participants to explain their tinnitus. One can

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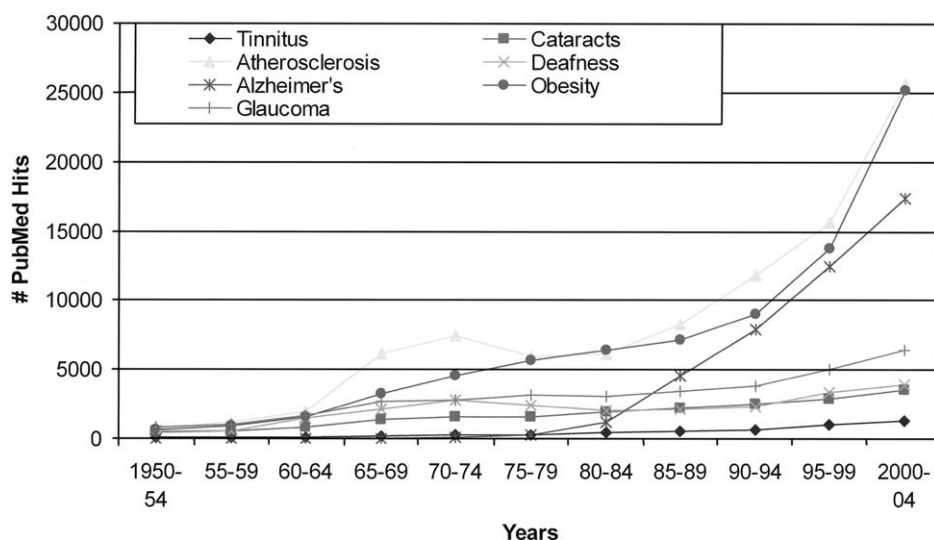


Fig. 1. Number of PubMed hits as a function of year for the search term “tinnitus” as well as a variety of other sensory conditions. Even though tinnitus is much more common in the general population than either “glaucoma” or “cataracts”, the level of research produced on tinnitus is substantially less. Also surprising is the relatively flat research productivity on “deafness”. (See Color Plate 13.1 in color plate section.)

imagine how such a subjective assay might impede progress in the field. Consider how the progress of cardiology might have been different without the angiogram, or neurology without the MRI. Relying on a person, to explain the tightness in their chest and whether they feel like their heart has a problem would surely limit our ability to help these patients today. However, this is almost exactly what we do with tinnitus patients. The inherent difficulty of collecting scientific measurements of the subjective experience of tinnitus in humans is daunting enough, but how then do we tackle such a subjective personal experience in an animal model? The difficulty in measuring tinnitus in both humans and in animal models has been an almost disabling obstacle to our understanding of the mechanisms of tinnitus, and it is reflected in the scientific literature.

The basic dilemma faced by the animal researcher, who wants to study tinnitus is whether or not their animals have tinnitus. In the end, it is of little interest to the researcher if there is a clear change in a certain neurotransmitter, or electrophysiological changes in a particular brain structure if those changes are not the results of tinnitus but rather the result of hearing loss or some other

factor. It is not merely enough to assume that manipulations associated with tinnitus in people cause tinnitus in laboratory animals. Whether we are talking about producing tinnitus in animal models through noise exposure, salicylate administration or some other mechanism, it is a pretty significant leap-of-faith to assume that animals will respond the same way humans do. In addition to being purely correlational in nature, such an approach is flawed because we really do not know what causes tinnitus in people, so making generalizations from humans to rodents in this case might be particularly problematic. Rather, it is becoming increasingly clear that some behavioral verification that experimental animals have tinnitus is needed. What a fascinating challenge to behavioral neuroscience — to find a way to have a rat tell you about the ringing in its head.

At its core, the purpose of the current article is to address this simple question, what tools have researchers developed to tell that an animal is hearing something inside its head? On the surface, developing such a tool seems an almost impossible task given the limited communication abilities of the kind of animal mostly used in neuroscience, namely rodents. Indeed, this question has proven

to be a difficult one for behavioral neuroscientists to address. Nevertheless, several methods have been proposed for assessing tinnitus in rodents (see [Moody, 2004](#)). The focus of this article is to briefly summarize the different approaches investigators have taken to determine whether an animal model has tinnitus. This is not meant to be an exhaustive account of each method, nor is it meant to be an overly critical evaluation of the strengths and weaknesses of each approach. Currently there is still very little published about most of these methods so such a critical review will have to wait until the scientific literature is mature enough to make such a review possible.

Most of the models that have been published require training animals to respond in some manner to silence, inducing tinnitus and then showing that tinnitus is present by errors in “silent” trials, suggesting the animal now hears something when external sounds are absent. The first published description of an animal model for tinnitus was that by Jastreboff et al. (1988). Many replications and extensions of that work have been done using basic mechanisms of conditioning ([Bauer et al., 1999](#); [Heffner and Harrington, 2002](#); [Guitton et al., 2003](#); [Ruttiger et al., 2003](#); [Lobarinas et al., 2004](#); [Heffner and Koay, 2005](#)) (see also Chapter 12). Recently, a model using reflex modification has been developed to assess whether the auditory system of animals suspected to have tinnitus could effectively code silence ([Turner et al., 2006](#)). This chapter will describe this model after a brief summary of the extant behavioral measures of tinnitus in the literature.

Jastreboff et al.’s conditioned lick suppression procedures

The method developed by Jastreboff et al. (1988a, b) makes use of a form of operant conditioning first introduced by [Estes and Skinner \(1941\)](#) to study the development of fear and anxiety. Estes and Skinner’s approach (commonly referred to as conditioned suppression) involved first training rats to press a bar for food. What they found then was that by presenting a tone paired with shock enough times, eventually presenting the tone alone was

enough to suppress the bar pressing behavior. The tone came to serve as a fear cue to the animal that inhibited ongoing behavior. Indeed, the primary behavior change after the fearful tone was introduced was freezing, which is of course incompatible with pressing a bar, eating, drinking and other behaviors. Before its application to tinnitus, Estes and Skinner’s conditioned suppression methodology was used to determine auditory thresholds in a variety of species ([Sidman et al., 1966](#); [Dalton, 1967](#); [Price et al., 1967](#); [Masterton et al., 1969](#); [Smith, 1970](#)). Jastreboff’s insightful application of these conditioned suppression procedures to tinnitus involved training animals to associate *silence* (rather than a tone) with a resulting shock. After sufficient pairings of the silence with a shock, the silence would begin to be associated with fear responses in the animals. The fear could be measured in several ways, such as freezing behavior or the cessation of bar pressing, eating or drinking behavior in hungry or thirsty animals. Jastreboff used water restriction to motivate the animals to lick from a waterspout. Then, the animals would be trained to stop licking when a background sound was turned off by pairing the silence with foot shock. Tinnitus could then be introduced with salicylate and experiments could measure whether these animals exhibited the same level of fear (suppression of licking behavior/freezing). The major measure of interest in this model then became the rate of extinction between trained animals and control animals without salicylate over a 5–10 day period. In this model tinnitus is assumed to be present if the treated animals’ lick suppression extinguished more rapidly. That is, animals with tinnitus began to lick earlier than controls during the quiet intervals. In this model, Jastreboff and colleagues have demonstrated that such animals act as if they do not hear silence and continue to lick. Apparently, their internal tinnitus served as a sufficient cue that kept them from hearing the silent cue being presented to them. A summary of the approach used by Jastreboff and colleagues to measure tinnitus can be found in [Fig. 2](#).

In subsequent studies, the experimental paradigm has been altered slightly to address a variety of experimental questions. For example, very different results are obtained when the order is

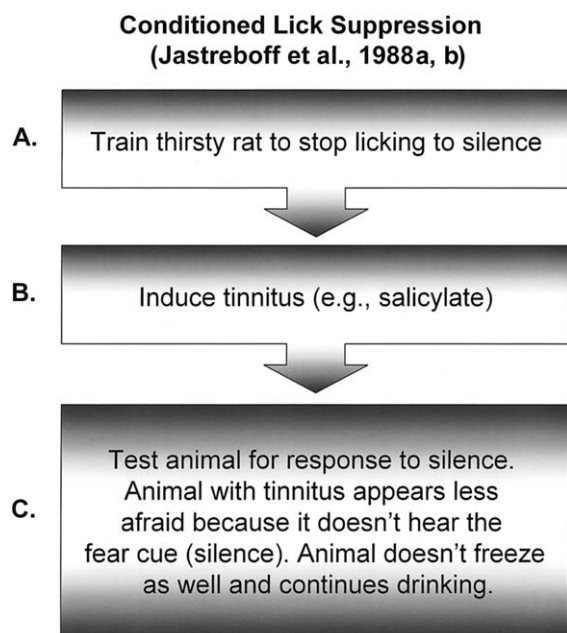


Fig. 2. Summary of the initial behavioral model developed by Jastreboff et al. (1988). Many variations of this basic strategy have been employed in subsequent studies.

reversed and animals are first given tinnitus then trained to associate silence with a shock. As these animals do not officially hear silence they are actually being trained to associate the sound of their tinnitus (silence) with the foot shock. Effectively, this paradigm trains the animals to fear their tinnitus. This fear, however, extinguishes quite easily outside of the experimental training because their tinnitus is continuous. In an attempt to control this, a continuous background noise is typically employed both in the housing and testing chamber.

While these studies pairing tinnitus with shock were done initially in the attempt to further refine this model, this approach has much to offer the field by way of helping to clarify the emotional/limbic system involvement in tinnitus (Wallhauser-Franke et al., 2003; Zhang et al., 2003; Muhlau et al., 2006). A cursory review of the current behavioral methods for assessing tinnitus makes it very clear that aversive events are an almost ubiquitous feature of these models. Most models include some aspect of fear/emotionality by using shock, food or water deprivation or some other aversive event. There is considerable animal research on the

brain mechanisms of fear conditioning (e.g., Davis, 1990; LeDoux, 2000) that tinnitus researchers using these behavioral models might be able to use to begin understanding the troubling emotional components of tinnitus.

Jastreboff and colleagues have provided several replications and extensions of their initial work. For example, hearing loss as an explanation for their findings has been largely ruled out (Jastreboff et al., 1988b; Jastreboff, 1989, 1990). Inducing tinnitus with means other than salicylate, such as with quinine, has also been done (Jastreboff et al., 1991). An additional extension of this work was to show that it might be useful for measuring the pitch and intensity of tinnitus. For these applications, Jastreboff and colleagues made use of the principle of discrimination. If an animal is trained to fear a particular sound frequency, then it will show the greatest fear to tones of that frequency and as the frequency of the stimulus becomes more and more different, the associated fear is also reduced. In such experiments animals are first given tinnitus by administering salicylate, then trained by pairing silence (their tinnitus) with shock and then presented with a variety of background sounds from low to high pitch. Whatever frequencies are associated with the most suppression (fear) are likely to be those that closely resemble their tinnitus. So, if a rat experiences tinnitus at 10 kHz, and its tinnitus is paired with shock, then when that rat is brought back later and given a 10 or 11 kHz background sound, its behavioral suppression should be substantial. However, if the background sound is of a much lower or higher frequency than the tinnitus, then it will not be associated with fear and might possibly serve as a safety signal and the animal's behavior will not be suppressed. Using this procedure, Jastreboff and colleagues suggested that salicylate-induced tinnitus in rats is experienced around 10–11 kHz (Jastreboff and Sasaki, 1994).

Bauer/Brozoski's conditioned lever pressing/suppression procedure

The Bauer/Brozoski model (Bauer et al., 1999; Bauer and Brozoski, 2001) is similar to that of

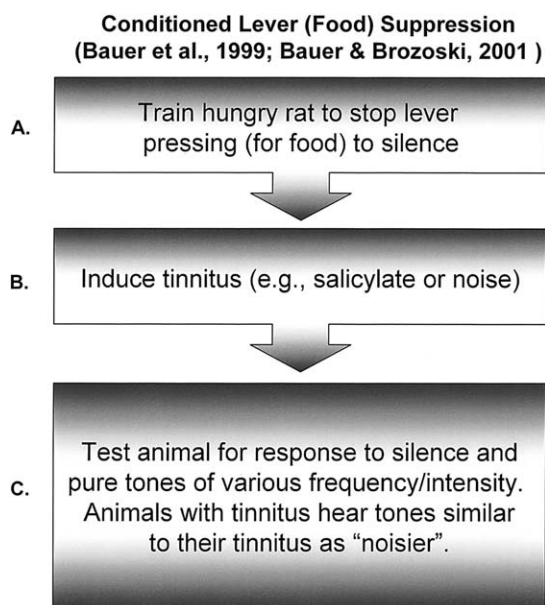


Fig. 3. Summary of the behavioral model developed by Bauer et al. (1999) and Bauer and Brozoski (2001).

Jastreboff et al. in that animals are trained to stop responding when silence is presented to the animal (Fig. 3). Jastreboff's animals are thirsty and are trained to stop licking when silence is presented while Bauer/Brozowski's animals are hungry and are trained to stop pressing a lever for food when silence is presented. Both models use a mild foot shock if the animal fails to stop responding (licking or lever pressing) during the silent period. The Bauer/Brozowski model also presents other stimulus conditions containing tonal stimuli of various frequencies and intensities. Animals with suspected tinnitus show a frequency specific shift in discrimination functions suggesting that animals hear tones similar to their tinnitus as "noisier" because of their tinnitus (Bauer et al., 1999). As with the Jastreboff technique, very different responses are obtained whether training is done before or after inducing tinnitus. Obviously, if animals are first given tinnitus then trained to stop bar pressing during quiet intervals, then they are really being trained to stop bar pressing when all they hear is their tinnitus. Conversely, if animals are first trained to stop lever pressing during silent intervals, then tinnitus is induced, a deficit in

hearing silence would be expected. Understanding this point is critical to appreciating the contributions of the work of Bauer/Brozowski's model. Two major contributions of the Bauer/Brozowski method is that it has been used to detect *chronic* tinnitus resulting from noise exposure (which is more problematic than acute tinnitus to humans) and it can be used in animals over long periods of time allowing a greater amount of data to be collected. Some animals have been repeatedly tested for up to 17 months after unilateral noise exposure with this method and their tinnitus seems to persist and possibly even intensify over time (Bauer and Brozoski).

Guittton et al.'s conditioned pole jumping avoidance procedures

Guittton and colleagues (2003) proposed a different method for assessing tinnitus in behaving animals (see Chapter 12). Rats were trained to jump onto a pole whenever they heard a 10 kHz, 50 dB SPL pure tone. A foot shock was used to encourage the animal to jump onto the pole when the sound was turned on. The 10 kHz signal was chosen because of prior work suggesting salicylate-induced tinnitus in rats is experienced as an approximately 10 kHz sound (Jastreboff and Sasaki, 1994). After rats are trained to jump on the pole in response to a 10 kHz signal, they are then given salicylate to induce tinnitus. When these rats are then placed into the testing apparatus they jump onto the pole erroneously during the silent periods because they "hear" a 10 kHz sound (Fig. 4).

Ruttiger et al.'s conditioned liquid reward procedures

In an attempt to avoid food and water restriction and use only minimal aversive stimuli, Ruttiger et al. (2003) developed a model for assessing tinnitus in rats that provided sugar water rewards during white noise stimuli and no rewards during silence. The measure of interest was whether the animals attempted to access the liquid feeder. Photo sensors were used to determine whether a rat stuck its nose into the trough to drink sugar

Conditioned Pole Jumping Avoidance (Guitton et al., 2003)

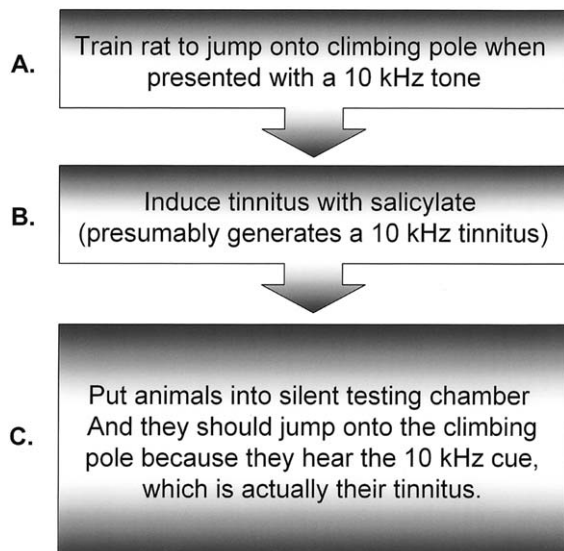


Fig. 4. Summary of the behavioral model developed by Guitton et al. (2003).

water. Administration of drugs to induce tinnitus was then done and it was assumed that animals with tinnitus would attempt to access the sugar water even during the quiet trials. The best explanation for these results is that the presence of the tinnitus in the quiet trials was interpreted as an acoustic signal suggesting sugar water could be accessed (Fig. 5).

Lobarinas/Salvi et al.'s conditioned polydipsia suppression procedure

Lobarinas et al. (2004) proposed a model for assessing if animals had tinnitus that involved first food restricting rats, then delivering a food pellet at regular intervals (approximately 1 min). Scheduled food delivery induces a natural, high rate of licking for water between each pellet, referred to as polydipsia. At that point, a shock avoidance paradigm was used such that animals were allowed to freely lick between food pellets in quiet but whenever one of six sounds was present and it licked the spout, a shock was presented. The shock served to effectively suppress the licking and with training

Conditioned Lick Reward Procedure (Ruttiger et al., 2003)

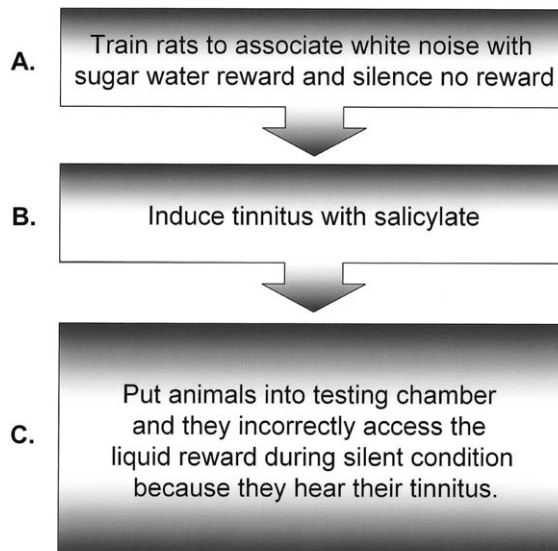


Fig. 5. Summary of the behavioral model developed by Ruttiger et al. (2003).

the animals learned to stop licking whenever a sound was presented. Their results suggested that animals that are then given salicylate, quinine or noise exposure to induce tinnitus (Lobarinas et al., 2004; Lobarinas et al., 2006; Yang et al., 2006) would act in quiet intervals as if a sound was present; that is, they suppressed their licking during quiet intervals (Fig. 6). This procedure allowed for relatively stable collection of data from individual rats. In addition, because the shock in this model was always associated with licking during a sound, the response was not quickly extinguished as in the Jastreboff model and allowed for data to be collected over extended periods of time.

Heffner et al.'s conditioned Two-Choice Left/Right Procedure

Before discussing Heffner's Two-Choice Left/Right Procedure, we should mention that Heffner first described a procedure for assessing tinnitus that was very similar to some of the previously described procedures. In fact, Heffner was involved in some of the earliest applications of

Conditioned Polydipsia Avoidance Procedure (Lobarinas et al., 2004)

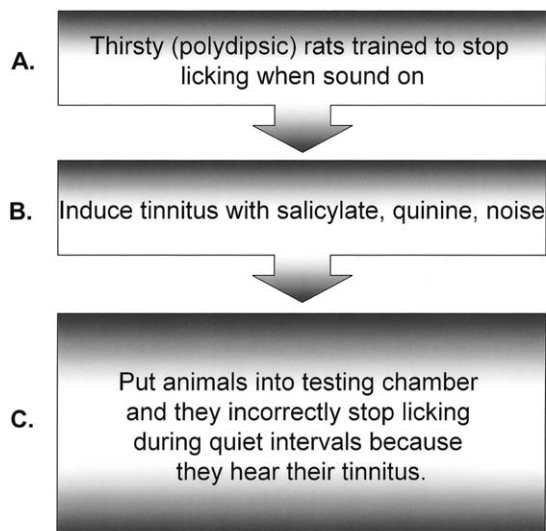


Fig. 6. Summary of the behavioral model developed by Lobarinas et al. (2004).

conditioned suppression to study auditory thresholds (Masterton et al., 1969). Briefly, Heffner and Harrington (2002) trained hamsters to lick in the presence of sound but to stop licking during quiet or a shock would ensue. The measure of interest was the fraction of time the animal was in contact with the licking spout in the sound and quiet conditions. Hamsters were then given a unilateral 10 kHz trauma to induce tinnitus. As expected, and similar to many of the previous methods, animals responded in the quiet conditions as if a sound was present. That is, they made contact with the licking spout because their tinnitus served as a false cue that a sound was present.

Heffner's more recent tinnitus model involved first training hamsters to lateralize sounds (Heffner and Koay, 2005). To do this, animals were presented with trials consisting of either quiet or a sound from either the left or right side. Thirsty hamsters (water was only available during daily training and testing) were given a water reward if they turned to the appropriate side that the sound came from. Attempting to lick from the incorrect side (no sound side) resulted in a mild shock between the sipping tube and cage floor. The animal

Conditioned Two-Choice Left/Right Procedure (Heffner & Koay, 2005)

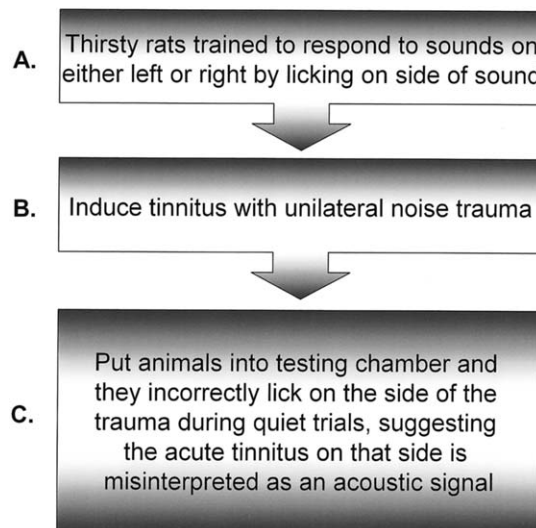


Fig. 7. Summary of the behavioral model developed by Heffner and Koay (2005).

was then given a unilateral noise trauma to induce tinnitus and put back into the testing apparatus. The general finding was that exposed animals shifted their responding on the silent trials to the side of their exposed ear. Their tinnitus on the side of the noise exposure just prior was misinterpreted as a physical signal emanating from that side (Fig. 7). While this task allowed for each animal to serve as its own control and minimized the need for group data, it appears best suited for measuring acute, unilateral noise-induced tinnitus. In addition, it would be ineffective at measuring bilateral tinnitus that might result from salicylate or chronic tinnitus following noise trauma. However, Heffner and Koay noted that it would be possible to adapt the task to measure bilateral tinnitus by training animals to go to one side in the presence of sound and to the other side during quiet (Heffner, 1983).

Moody's proposed approach

While details have not yet been published in a peer-reviewed journal, Moody (2004) suggested an

additional approach to testing for tinnitus in animals. He proposed that guinea pigs should be trained to respond on one lever when a sound was turned on and on a different lever during quiet intervals. By comparing responses to the two levers before and after administration of an agent that was to be tested for its ability to cause tinnitus, he suggested it might be possible to measure the presence of tinnitus. This approach would be similar to that proposed by [Heffner and Koay \(2005\)](#) to detect the presence of bilateral tinnitus.

Turner et al.'s unconditioned gap detection startle reflex procedure

Each of the previous models requires relatively complex behavioral manipulations that often include food or water deprivation, aversive shock and/or weeks-to-months of behavioral training that limits the efficiency of research and can be difficult and costly to implement. Additionally, because each of the previous methods rely heavily on learning, memory and motivation, studying tinnitus in aged animals where these mechanisms might be impaired, or designing drug studies that might also impact these processes, becomes problematic.

To address some of these concerns, [Turner et al. \(2006\)](#) proposed a model, which does not require learning and makes use of the acoustic startle reflex. The model essentially probes the auditory system using a reflex to determine whether it can register a silent interval normally. The model is based upon the ubiquitous property of the startle reflex to be reduced in magnitude by a preceding silent gap in an otherwise continuous acoustic background. In normal hearing animals, when a silent gap is presented just before (100 ms) a startle stimulus, the response to the startle stimulus is reduced in magnitude. Turner et al. hypothesized that when the background sound in which the silent gap was embedded was qualitatively similar to the animal's tinnitus, worse detection of the silent gap would occur because the animal's tinnitus filled in the silent gap. The results of implementing this model confirmed the

hypothesis and animals with prior evidence of tinnitus at 10 kHz (using the behavioral methods of Bauer/Brozoski) were shown to have deficits in reacting to a silent gap embedded in an otherwise continuous 60 dB SPL, 10 kHz background (1000 Hz bandpass). No significant gap-detection differences were found between tinnitus and control animals with either 16 kHz bandpass signals or broadband noise (BBN) backgrounds, supporting the hypothesis that an animal with tonal tinnitus will show impaired gap detection in an acoustic environment with features resembling its tinnitus. A variety of control procedures have been done to verify that the gap detection deficits were the result of tinnitus and not hearing loss or some other explanation ([Turner et al., 2006; Fig. 8](#)).

In addition to cross validating the measure with the tinnitus method of Bauer and Brozoski ([Turner et al., 2006](#)), it has also recently been validated against the schedule-induced polydipsia method of Lobarinas/Salvi ([Yang et al., 2006](#)). With further refinement, gap detection deficits measured using the reflex methodology may serve as a valuable tool in the study of tinnitus. However, additional work is needed to verify that what was measured by this technique was tinnitus and not some artifact of tinnitus and/or hearing loss. If additional work continues to support that this procedure is measuring tinnitus, several benefits of this method become apparent. The most obvious is its ability to rapidly screen for tinnitus in many animals because a reflex is used, rather than having to spend weeks conditioning animals. In fact, it is currently possible, within 1 h, to determine whether up to eight otherwise naïve (to the testing apparatus) rats have signs of tinnitus and in what frequency range. Considerable data can be obtained from single animals since the response does not extinguish like a learned response would. No food, water or shock is used so concerns related to satiety or presenting aversive events are minimized. In addition, repeated, long-term testing becomes possible as startle reflex procedures have been used to follow chronological changes in single animals for well over a year ([Willott and Turner, 1999](#)), although not yet for tinnitus.

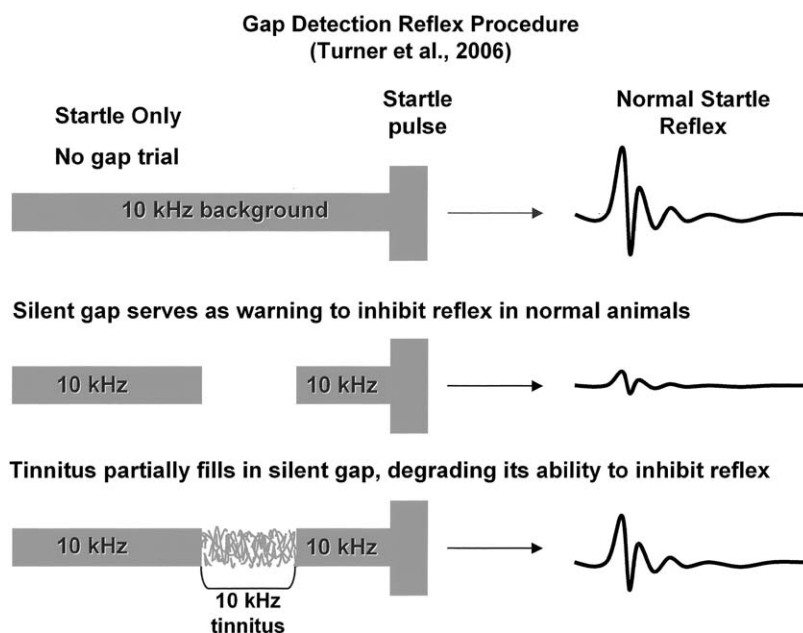


Fig. 8. Summary of the behavioral model developed by Turner et al. (2006).

Conclusions

Measuring tinnitus behaviorally in animals can be a very expensive, time consuming and an exceedingly complex and tedious process. It takes a psychologist schooled in classical and operant conditioning theory to truly appreciate the fine details of many of the studies outlined in this chapter. The fact of the matter is that without one of the listed authors working as a co-investigator, it would currently be very difficult for a tinnitus researcher who is not a psychologist to adopt any one of these procedures. This same problem used to exist for researchers in many other areas. Today however, the typical Alzheimer's researcher no longer has to be a psychologist to understand behavioral data collected using a shuttlebox, Morris water maze or a T-maze. The pain researcher does not have to have a Ph.D. in psychology to use a hot plate. Behavioral equipment in many other areas of study is commercially available and protocols are widely available. Tinnitus research could benefit from a similar movement towards behavior.

Through the work of a handful of creative scientists there are now a variety of options available to tinnitus researchers and rather than try to rank one method over another, it is important that multiple behavioral measures are used in the field. There are obviously some measures discussed here that are better suited to address certain experimental questions. For example, the left/right laterality method of Heffner and Koay (2005) seems particularly well suited to investigate the mechanisms of acute noise-induced tinnitus. With careful experimental design modifications, any of the conditioning-based procedures using aversive events (Jastreboff, Bauer/Brozski, Guitton, Lobarinas/Salvi) could be used to identify the limbic/emotional components of tinnitus. Because each of these previous methods (as well as that of Ruttiger) involves conditioning, they might also be used to tap into some of the more cognitive features of tinnitus. The procedure of Turner et al. (2006) seems well suited for rapid measures of the more sensory aspects of tinnitus that can be measured in a reflex, rather than the more cognitive/perceptual aspects that might require full awareness and

attentional processes of the animal. Finally, for investigators wishing to use conditioning methods and to avoid food/water restriction, the reward-based procedure of Ruttiger et al. is probably the most appropriate. Regardless of the method used, it is the hope of this author, that greater use of appropriate animal models, will facilitate research in tinnitus.

Acknowledgments

Supported in part by NIH grant DC008357 to JGT. Thanks to Jennifer Parrish for help preparing this manuscript.

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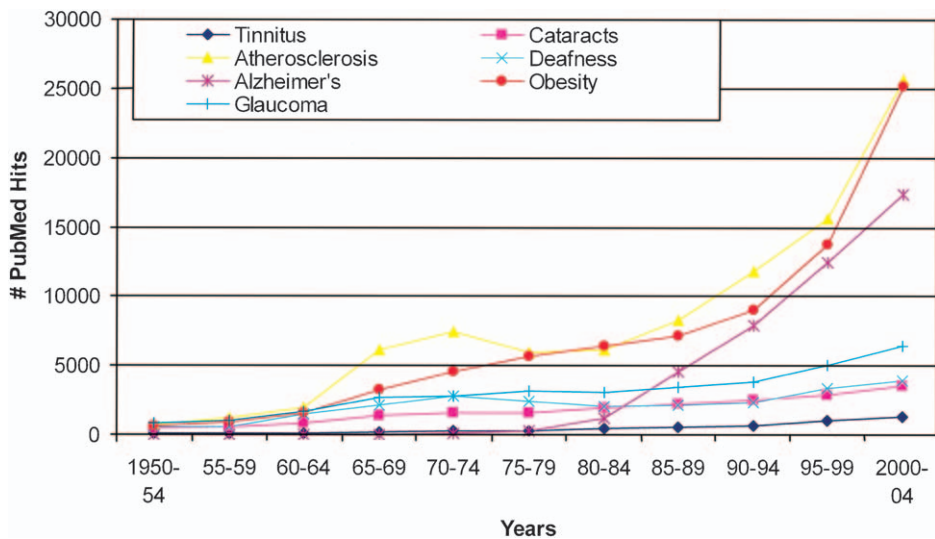


Plate 13.1. Number of PubMed hits as a function of year for the search term “tinnitus” as well as a variety of other sensory conditions. Even though tinnitus is much more common in the general population than either “glaucoma” or “cataracts”, the level of research produced on tinnitus is substantially less. Also surprising is the relatively flat research productivity on “deafness”. (For B/W version, see page 148 in the volume.)

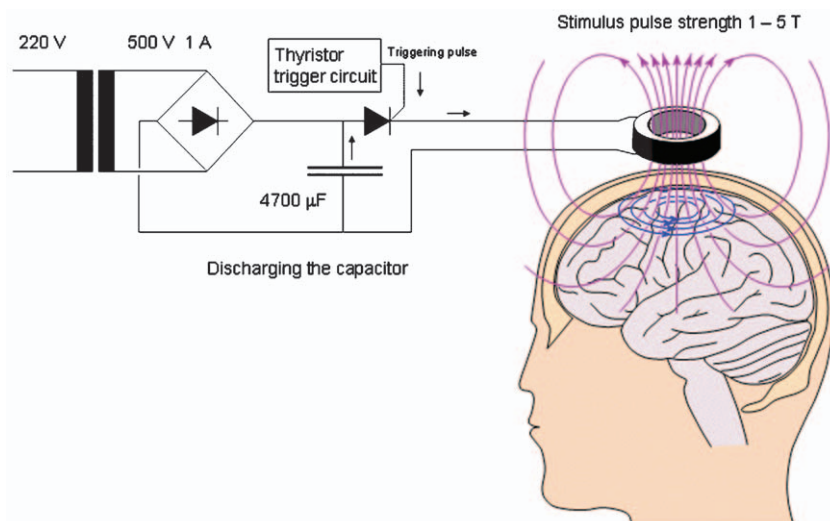


Plate 34.1. The principle of TMS with symbolized spread of magnetic fields perpendicular to the coil windings (Adapted with permission from Jaako Malmivuo and Robert Plonsey: Bioelectromagnetism — Principles and Applications of Bioelectric and Bio-magnetic Fields, Oxford University Press, New York, 1995). (For B/W version, see page 360 in the volume.)

CHAPTER 14

Genetics of chronic tinnitus

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Abstract: Susceptibility to chronic tinnitus is highly variable and of particular interest when it comes to defining strategies for prevention and treatment. While several rare monogenic disorders have been described that are associated with tinnitus, the genetic underpinnings of the more common forms of the syndrome are still poorly understood. The present article incorporates recent advancements in the field, including the epidemiology of tinnitus in subjects with neuropsychiatric illness, and highlights pilot studies of candidate genes.

Keywords: tinnitus; genetic risk; endophenotype; biomarker

Introduction

Tinnitus is a highly prevalent condition and an unresolved issue in population health. Estimates suggest that approximately one in eight Americans, Australians and Europeans, and one in ten Chinese suffers from chronic tinnitus (Seidman and Jacobson, 1996; Xinhua Online Report, 2005; Humes et al., 2006) (see also Chapter 1). The magnitude of the problem has led to the worldwide formation of numerous self-help groups over the past decades, to the initiation of surveillance programs, and to the coordination of research by large nonprofit organizations such as the American Tinnitus Association (ATA) founded in 1971. The economic impact of tinnitus on the general population has not been estimated to date (Henry et al., 2005), but the urgency of understanding the underpinnings of tinnitus is illustrated by \$190 million in compensation payments awarded in

2004 to US veterans with tinnitus as their major disability (Humes et al., 2006).

Despite a growing interest in reducing the burden associated with tinnitus, the individual susceptibility to the condition has received little attention. Many environmental risk factors have become known, notably medications (e.g., salicylates or aminoglycoside antibiotics), stressful life events, noise exposure or head injury. Only certain individuals, however, will develop tinnitus in the presence of the above risks, and others may develop symptoms without known precipitants (Chapter 1). In one survey of individuals with tinnitus, close to 50% of the participants did not attribute their tinnitus to any particular cause (Stouffer and Tyler, 1990). The reasons behind this variable response to environmental cues and behind the liability to endogenous forms of tinnitus are poorly understood. Variability extends to additional features of tinnitus: its onset may be gradual or sudden (Sindhusake et al., 2003), and it may occur together with disorders of the inner ear, affective disorders (Chapter 20) or specific disorders such as Ménière's disease. Treatment outcome

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is often difficult to predict (Chapters 48 and 49). Research also indicates that tinnitus-coping patterns (Chapters 40 and 41) and personality traits (Chapter 20) play a major role in the perceived severity of tinnitus (Axelsson and Sandh, 1985) and in the progression of symptoms (Olderog et al., 2004).

With only a limited number of treatment options currently available to individuals affected by tinnitus, there is an obligation to identify predisposing factors. Translation of this information to strategies for preventing some forms of tinnitus will eventually help reduce morbidity and, hopefully, pave the way for restoring silence to victims' minds, i.e., improve quality of life.

History

The search for traits that confer an increased risk of developing chronic tinnitus is complicated by phenotypic heterogeneity and by variable penetrance of the syndrome. Progress has been swift in the setting of monogenic disorders associated with secondary chronic tinnitus where causative genes have already been identified (Table 1). In contrast, the search for genetic risk factors for the more common forms of chronic primary tinnitus is still in its early stages. As of April 2007, precise data on heritability are lacking given the absence of family and twin studies, and very few anecdotal reports on familial primary tinnitus. Public awareness of heritable forms of tinnitus, however, is strong and major US cryobanks have included tinnitus-specific inquiries in their interviews of sperm donors (Plotz, 2006).

Paucity of scientific evidence with respect to the genetic risk of chronic primary tinnitus may be due to several factors: First, difficulties have long been encountered in defining chronic tinnitus, and in assessing the various phenotypes. Diagnostic consensus criteria are only gradually emerging (McCombe et al., 2001) and competing tools for subjective ratings of tinnitus-related complaints have been in use (Henry et al., 2005). As a result, a deficit exists in epidemiologic data from individuals with chronic tinnitus and regarding detailed information on family histories of tinnitus. Despite

the large number of medical specialties that may be involved in the diagnosis and treatment of chronic tinnitus, very limited information is available on early onset tinnitus (Holgers and Juul, 2006), a condition that may be more heritable than late-onset forms of the syndrome. Finally, as with many common diseases, diathesis is likely obscured by a complex mode of inheritance in chronic primary tinnitus, as opposed to the rare monogenic forms of secondary tinnitus. It is anticipated that non-Mendelian patterns of inheritance will reduce the awareness of family members being affected by tinnitus and lead to underreporting of disease prevalence among relatives.

Current strategies

In view of missing genome maps for the targeting of chromosomal regions in families affected by chronic primary tinnitus, alternative strategies are being chosen for genetic investigations. The rationales adopted include: (a) the focusing on candidate molecules that hold promise as tinnitus biomarkers and (b) the use of additional phenotypic parameters that may aid in identifying tinnitus endophenotypes. To a large extent, both strategies will benefit from stringent diagnostic criteria to dissect the various forms of the illness, and from implementation of systematic clinical assessments.

The biomarker approach

A number of putative tinnitus biomarkers have been derived from investigations of structures controlling auditory processing, e.g., using studies of gene expression in animal models (Liang et al., 2006). Thus a number of observations favor a prominent role of the serotonergic system in auditory perception and in the etiology of tinnitus (Simpson and Davies, 2000). These comprise the modulation of auditory evoked potentials (AEPs) by selective serotonin reuptake inhibitors (SSRIs) (Gopal et al., 2005) and the presence of serotonergic fibers in several auditory nuclei in the central nervous system (Thompson and Lauder, 2005). While screening for mutations in genes

Table 1. Monogenic disorders associated with secondary chronic tinnitus

Monogenic disorders associated with chronic tinnitus	Mutated gene (chromosomal locus)
Dentinogenesis imperfecta	<i>DSPP</i> (4q21)
Hereditary motor and sensory neuropathy (HMSN) VI	<i>MFN2</i> (1p36)
Familial paragangliomas 1	<i>SDHD</i> (11q23)
Neurofibromatosis type II	<i>NF2</i> (22q12)
Familial paragangliomas 3	<i>SDHC</i> (1q21)
Familial paragangliomas 4	<i>SDHB</i> (1p36)
Episodic ataxia type II	<i>CACNA1A</i> (19p13)
Von-Hippel-Lindau syndrome	<i>VHL</i> (3p25)
Kanzaki disease	<i>NAGA</i> (22q11)
Low frequency sensorineural hearing loss (LFSNHL)	<i>WFS1</i> (4p16)
Osteogenesis imperfecta type I	<i>COL1A1</i> (17q21), <i>COL1A2</i> (7q22)
Fabry disease	<i>GLA</i> (Xq22)
Autosomal dominant nonsyndromal sensorineural deafness	<i>COCH</i> (14q12)

encoding serotonin (5-HT) receptors in individuals with chronic tinnitus has been initiated (Kleinjung et al., 2006b), the complex interplay of serotonergic signaling and other effectors argues against limiting the approach to a single neurotransmitter system. Moreover, the direct involvement of 5-HT in the transduction of pure tones during auditory processing is being questioned (Bartolome and Gil-Loyzaga, 2005), and the utility of recorded AEPs as a surrogate marker of central 5-HT function is a matter of debate (Dierks et al., 1999). In an association study involving >400 individuals genotyped for a functional length polymorphism in the regulatory region of the 5-HT transporter gene (*5-HTTLPR*), no significant effect was noted on susceptibility to chronic tinnitus (Sand et al., 2006a). This could indicate an indirect, rather than a direct, modulatory role of 5-HT in tinnitus etiology and central nervous adaptive mechanisms (see Chapter 2).

Evidence has accumulated over the past decade to account for 5-HT's participation in the maintenance and regrowth of neurones in the adult brain (Sodhi and Sanders-Bush, 2004). Specifically, the interplay of 5-HT transmission and neurotrophic factors (Eaton et al., 1995) warrants further investigation in the maintenance and restoration of auditory function. Neurotrophins have emerged as mediators of peripheral neuronal remodeling (Shinohara et al., 2002; Walshe et al., 2003), and as mediators of tonotopic organization

in the central auditory pathway (Staecker et al., 1996; Reser and Van de Water, 1997). Animal models of brain-derived neurotrophic factor (BDNF)-dependent sensory, cortical and hippocampal structural change testify to the implications of defective neuroregeneration for auditory phenotypes (Morris et al., 2006). Furthermore, BDNF-induced changes in glutamatergic signaling suggest modulatory effects on spontaneous neuronal firing rates in the auditory cortex (Lessmann, 1998; Kaltenbach, 2000). In a study addressing the *BDNF* gene, a significantly lower risk of developing chronic tinnitus with hearing impairment was observed among carriers of a *BDNF* Val66Met missense variant relative to other individuals (Kleinjung et al., 2006a). Finally, brain structural change, a downstream correlate of neurotrophin functionality, has recently been proposed as the long-sought common denominator of different auditory phantom sensations (Muhlau et al., 2006).

In addition to being guided by the use of human brain imaging and animal models, the search for biological pathways and candidate genes for tinnitus has come to rely on the individual response to drugs. Among the pharmacological treatments available to tinnitus sufferers count agents that are in use for the management of mood disorders (Zoger et al., 2006a). Subjective benefits after the intake of anxiolytic and antidepressant medication for tinnitus complaints have suggested that SSRIs may also hold the key to understanding the

underlying pathophysiology (Sullivan et al., 1993), e.g., via SSRI-induced changes in neurotrophic factor expression (Chen et al., 2001; Warner-Schmidt and Duman, 2006) (Chapters 23, 24). But the clinical response to SSRIs in chronic tinnitus is highly variable (Baldo et al., 2006) and it remains to be seen whether functional variation in genes encoding 5-HT homeostasis qualifies as a tinnitus risk factor (Tyler et al., 2006).

Nociceptin and other neuropeptides that have been implicated in nociception or sleep regulation may equally hold promise as biomarkers. Thus a limited number of participants have experienced benefits in trials of melatonin as a treatment for tinnitus (Rosenberg et al., 1998; Megwalu et al., 2006). In most cases, however, findings remain unconfirmed, e.g., with respect to delta-sleep-inducing peptide's utility in alleviating tinnitus (Larbig et al., 1984), or possible substance P-mediated effects on tinnitus sufferers presenting with headache (Vass et al., 2004).

The endophenotype approach

Many individuals suffering from tinnitus experience impaired emotional health, deficits in hearing, sleep, or concentration (Axelsson and Sandh, 1985; Hallberg and Erlandsson, 1993; Mrena et al., 2002; Tyler et al., 2004) (Chapters 1, 21, 41, 42). Assuming that concomitant conditions manifest on a common genetic background, this information can be used as a starting point for investigations of the genetic susceptibility to tinnitus. The incorporation of additional phenotypic parameters in the search for mutations specific to a disorder is a strategy widely used to overcome the difficulties posed by clinical definitions. There are, however, several caveats to be observed when an endophenotype-based approach is chosen. First, when disequilibrium between the target trait locus and the comorbid locus is low, association will not have sufficient power, and linkage is the better strategy for localizing genes. In this case, patterns of inheritance and phenotype cosegregation will need to be verified in affected families. Second, diagnostic assessment varies widely across studies and may be limited to the use of questionnaires

(Halford and Anderson, 1991; Folmer et al., 1999). The latter may prove helpful to quantify symptoms but the results obtained do not equate to diagnoses. Thus only few studies have been based on comprehensive psychiatric evaluations of individuals with tinnitus for identification of major depression (Table 2), as opposed to questionnaire-based studies of depressive mood, which are much less demanding both in terms of time and expertise. Finally, a lifetime diagnosis of a given comorbid trait is preferable over an acute diagnostic state evaluation.

As for major depression, higher lifetime prevalence rates have been reported in tinnitus sufferers when compared to controls (Harrop-Griffiths et al., 1987). Whereas current estimates of depression in the general population give lifetime rates of 6–25% (Weissman et al., 1991; Kessler et al., 1994; Spitzer et al., 1995; Lewinsohn et al., 1999), up to 61% of individuals with tinnitus have been diagnosed with depression (Sullivan et al., 1988; Holgers et al., 2005) while 49% of individuals with major depression report tinnitus (Mathew et al., 1981). Genome-wide scans of susceptibility to major depression have identified candidate regions on chromosomes 15q, 17p and 8p, among others (Holmans et al., 2007), which may, therefore, hold promise for a targeted search in tinnitus individuals. The neurogenic theory of depression provides a rationale for the association of emotional distress and chronic tinnitus by the respective impact of dysfunctional neural reorganization on limbic and auditory structures of the brain (Thomas and Peterson, 2003). Specifically, the role of BDNF in promoting plasticity-induced recovery has been emphasized in depression and depressive-like states (Angelucci et al., 2005; for a review, see Castren et al., 2007), in addition to its implication in auditory processing. Based on these observations, pilot studies of association have addressed genes encoding neurotrophic factors in chronic tinnitus and have lent support to the notion of a heritable neurogenic risk factor in a subgroup of affected individuals (Kleinjung et al., 2006a, 2007; Sand et al., 2006b).

Further evidence points at an association of specific tinnitus phenotypes, e.g., of symptom severity, with defined personality traits as measured

Table 2. Studies based on comprehensive psychiatric evaluations of individuals with tinnitus

	Comments	Study (N)	Criteria (instrument)
Comorbid mental diagnoses in subjects with tinnitus			
Major depression 62% (lifetime)		Harrop-Griffiths et al. (1987) (21)	DSMIII (NIMH DIS)
Alcohol abuse/dependence 48% (lifetime)			
Major depression 78% (lifetime)	Study may include patients from the preceding investigation	Sullivan et al. (1988) (40)	DSMIII (NIMH DIS)
Major depression 60% (current)			
Major depression 4% (current)	Prevalence may be specific to career army personnel	Attias et al. (1993) (47)	DSMIII (non-structured psychiatric interview)
Major depression 33% (current)		Simpson et al. (1988) (24)	DSMIII-R (SCID)
All affective disorders 46% (current)	Includes dysthymia and major depression		
All anxiety disorders 29% (current)	Includes phobias, panic disorder, generalized anxiety disorder, and somatoform disorder		
All anxiety disorders 45% (current)	Includes social phobia, panic disorder, generalized anxiety disorder, somatoform disorder, and obsessive — compulsive disorder	Zoger et al. (2001), Holgers et al. (2005) (82)	DSMIII-R (SCID)
All affective disorders 61% (lifetime)	Includes dysthymia, mild to severe depression, and bipolar depression		
All affective disorders 39% (current)			
Alcohol abuse/dependence 4% (current)			
All anxiety disorders 29% (current)	Excludes subjects with bipolar disorder, suicidal ideation or social withdrawal	Marciano et al. (2003) (75)	DSMIV (MINI)
All affective disorders 27% (current)			
PTSD 87% (current)	PTSD prevalence in a traumatized control group was 29% (current)	Hinton et al. (2006) (52)	DSMIV (CAPS)
All anxiety disorders 59% (current)		Zoger et al. (2006a) (76)	DSMIV (SCID)
All affective disorders 84% (current)			
All anxiety disorders 45% (current)	Study may include patients from the preceding investigation	Zoger et al. (2006b) (80)	DSMIV (SCID)
Major depression 33% (current)			
Other comorbid conditions			
TMJD 60% (current, case study)		Bernhardt et al. (2004) (30, 139)	Standardized clinical examination
TMJD 31% (current, cross-sectional study)			
Primary headache 63% (current)	Includes subjects with tension headache, mixed headache, cluster migraine, basic migraine, migraine with and w/o aura	Farri et al. (1999) (112)	International Headache Society standards

Notes: CAPS = Clinician-Administered PTSD Scale (Blake et al., 1995); DSMIII, III-R, IV = Diagnostic and Statistical Manual of Mental Disorders (3rd ed., 3rd ed. revised, 4th ed.) (APA, 1980, 1987, 1994); MINI = Mini International Neuropsychiatric Interview (Sheehan et al., 1998); NIMH DIS = National Institute of Mental Health Diagnostic Interview Schedule (Robins et al., 1981); SCID = Structured Clinical Interview (for DSMIII-R and DSM IV, respectively) (Spitzer et al., 1990; First et al., 2002).

by self-report questionnaire (see Chapter 20). This suggests a dual role of genetic traits involved in shaping personality dimensions, or the existence of genetic traits relevant to tinnitus in physical proximity to loci that determine personality. Adoption, twin and family studies have long confirmed the importance of genetic influences on personality (Van Gestel and Van Broeckhoven, 2003). Estimates of heritability obtained from twin studies range between 0.40 and 0.60 (Bouchard and Loehlin, 2001) and the use of personality dimensions as behavioral endophenotypes of associated conditions has been advocated (Chiaroni et al., 2005; Savitz and Ramesar, 2006). While a limitation lies in the complexity of most personality constructs, identification of a core personality phenotype in tinnitus should facilitate the search for contributing innate factors. Specifically, there is consensus that personality impacts on the adaptation to tinnitus and the course of the illness (Hallam et al., 1984; Gerber et al., 1985–1986; Collet et al., 1990). Individual coping styles can thus serve as valuable surrogate markers of temperament. Maladaptive coping correlates strongly with anxiety and depression (Budd and Pugh, 1996), and an anxious temperament is a strong predictor of tinnitus-related distress (Langenbach, 2005) (Chapter 20). Whether specific coping styles segregate with heritable forms of tinnitus has not yet been addressed, but a modifier role of family history of tinnitus on the perception of tinnitus has been documented (Stephens et al., 2003). In a recent investigation of 25 individuals with a family history of tinnitus, 28% felt that their own perception of tinnitus was different from that of individuals without a positive family history (Kennedy and Stephens, 2006). Pending more detailed studies on coping in affected families, however, contributions made by environmental factors are unclear. A possible overlap of tinnitus vulnerability with a behavioral predisposition to maladaptive coping is evoked by comorbid post-traumatic stress disorder (PTSD) in 87% of individuals diagnosed with tinnitus, as opposed to 29% in a traumatized control population (Hinton et al., 2006).

With the exception of hearing impairment studies, few reports exist on somatic comorbidity in

chronic primary tinnitus (Holgers et al., 2005). Among the known conditions frequently associated with tinnitus counts chronic facial pain, and specifically, temporomandibular joint disorder (TMJD) (Camparis et al., 2005). Up to 60% of tinnitus individuals present with complaints relating to TMJD (Bernhardt et al., 2004). Again, stress, anxiety and depression are known to increase the risk of developing TMJD which, in turn, may increase the likelihood of developing chronic tinnitus (Morgan, 1992). Clustering of the above syndromes has also renewed the interest in disrupted 5-HT neurotransmission as a candidate mechanism in tinnitus, TMJD, and some common behavioral correlates (Herken et al., 2001; Salvainelli et al., 2003). So far, no genome-wide linkage data exist for TMJD and the clinical features of tinnitus occurring with TMJD have not been fully characterized.

Tinnitus has also been described in persons presenting with various forms of headache (Erlandsson et al., 1992; Bernhardt et al., 2005). In one case series, 63% of individuals suffering from primary headache were diagnosed with concomitant tinnitus (Farri et al., 1999), and tinnitus is a known risk factor for developing headache. In individuals with basilar-type migraine, a prevalence of 0.26 has suggested aberrant neural activity along the auditory axis and a central nervous etiology not necessarily related to vasospasm (Sturzenegger and Meienberg, 1985; Volcy et al., 2005). Clustering of these phenotypes warrants more detailed research into the genetic background of dually affected individuals in the light of emerging loci for familial subtypes of migraine on 19p, 1q and 2q (Colson et al., 2007).

Implications and outlook

The present review highlights several avenues of research in the genetics of chronic tinnitus and the obstacles encountered so far. It appears premature to expect translation of existing genetic findings to novel treatments in the near future (Martin and Raphael, 2003), as the identification of valid biomarkers that may guide research remains a difficult task (Savastano et al., 2007). To judge by

the evidence available, genes involved in extra-cochlear parts of the auditory system deserve close scrutiny. Specifically, conceptualization of chronic tinnitus as a disorder intimately related to neuronal repair holds promise as a preliminary track to identifying key molecules, plus the corresponding genes and mutations of interest (Gil-Loyzaga, 2005). The interplay of many compounds, e.g., antioxidants, with tinnitus symptomatology is only gradually being addressed, and is expected to shed further candidate risk factors. In summary, the road to discovery of genetic risk factors in chronic tinnitus is currently under construction. For it to become paved, epidemiological information will need to be expanded once the challenges posed by significant clinical variability have been surmounted.

Abbreviations

AEP	auditory evoked potential
BDNF	brain-derived neurotrophic factor
5-HT	5-hydroxytryptamine, or serotonin
5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter gene length polymorphic region
PTSD	posttraumatic stress disorder
SSRI	selective serotonin reuptake inhibitor
TMJD	temporomandibular joint disorder

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CHAPTER 15

Hyperacusis, sound annoyance, and loudness hypersensitivity in children

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Abstract: The objective of the present study was to estimate the prevalence of hyperacusis among school-aged children. We define hyperacusis as lowered loudness discomfort levels (LDL) associated with an abnormal annoyance to sounds. We used questionnaires, interviews, and estimates of LDL in a study of 506 children from 5 to 12 years of age from 15 different schools. Participants with LDL in the lowest 5th percentile were classified as having loudness hypersensitivity; an abnormal annoyance to sounds if they responded “yes” to the question “Are you bothered by any kind of sounds or noise?” could describe the sound, and were able to identify at least 10 sounds from a list of 20 as being annoying. Phonophobia was defined as a fear of sound. Children with LDL in the lowest 5th percentile typically had LDLs lower than 90 dB HL; 42% of the participants in this group were bothered by sounds and 3.2% had hyperacusis. Fifty percent of the participants with hyperacusis had tinnitus and mild hearing loss in the left ear was an associated risk factor. Phonophobia was experienced by 9% of the children. It is concluded that hyperacusis in children is prevalent, and should be considered in clinical examinations.

Keywords: hyperacusis; tinnitus; loudness annoyance; children; cross-over study

Introduction

We define hyperacusis an unusual (low) loudness discomfort level (LDL) associated with annoyance from normal sounds. This is similar to Baguley’s definition of hyperacusis as a lowered tolerance to ordinary environmental sounds (Baguley, 2003) (see also Chapter 1). Decreased LDL is a disorder of loudness perception. The name hyperacusis is sometimes used for describing abnormal loudness perception in general, which also may occur in connection with sound deprivation.

Altered perceptions of sounds often cause an impact on everyday life. Hyperacusis is described as a typical component of Williams Beurens syndrome (WBS) (hypercalcaemia); Williams syndrome (Klein et al., 1990) is a genetic disease caused by a deletion of an elastin allele on chromosome 7 occurring in 1 in 20,000 live births. It is characterized by multiple congenital anomalies such as cardiovascular disorders, high levels of serum calcium, mental retardation, and a hyper social behavior associated to loquacity (Lashkari et al., 1999). Autism is also often associated with intolerance to loud sounds although perhaps not to a degree that is classified as hyperacusis (Chapter 1). Among these children, hyperacusis

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might be so severe that activities such as urban trips or house duties are avoided (Martin et al., 1984). In the presence of sound stimuli, even at a moderate intensity, such as television and telephone ring, these children adopt a characteristic behavior of covering their ears with their hands (Einfeld et al., 1997).

Studies of the prevalence of hyperacusis in children have focused on children with specific diseases, such as Williams Syndrome (Klein et al., 1990), autism (Rosenhall et al., 1999; Khalfa et al., 2004), and spina bifida (Oen et al., 1997). Prevalence estimates range from 95% to 18% in disease groups and from 27% to 0% in control groups (see Table 1). These studies have based the diagnosis of hyperacusis on parents' impressions on their children sensitiveness to sounds collected as it has been communicated by questionnaires. Only (Khalifa et al., 2004) associated loudness hypersensitivity on classifying hyperacusis considering 80 dB HL as a cut off level.

Among adults, the few prevalence studies on this subject are listed on Table 2. The studies showing *p* prevalence between 8 and 23% were based on questionnaires only.

The aim of the present study was to evaluate the prevalence of hyperacusis in a population of children and investigate possible risk factors such as noise exposure, history of otitis media, otologic surgery, middle ear disease, vestibular symptoms and its association with tinnitus.

Methods

The participants for this study are the same as those of the study on tinnitus (Chapter 16) where the selection procedures are described. Hearing tests, interviews, data collection were also the same for the two studies and described in Chapter 16.

Loudness discomfort levels

It was observed in a pilot study that many children did not report discomfort during the examination even at the maximum audiometer output, which was (110 dB HL at 0.25 Hz; 120 dB HL from 0.5 Hz to 6.0 kHz, and 100 dB at 8.0 kHz). The values of discomfort used in calculation of the means and standard deviation for the children who

Table 1. Prevalence studies on hyperacusis on pediatric population

Author	Condition	N sample/ control	Mean age	Diagnosis based on	Prevalence (%)	Prevalence on controls (%)
Klein et al. (1990)	Williams syndrome	65/65	8 years	Questionnaire to parents: (1) Is your children presently frightened or bothered by sounds (y/n), if not (2) Was this a past problem? (3) Asked to check if any of 20 sounds presented on a list disturbed their child, (4) Asked to describe child's reactions to sounds, and (5) the type of sound that triggers adverse reactions.	95	12
Oen et al. (1997)	Spina bifida	50/19	0–6 months	Oral interview and questionnaire to parents about reactions to sounds (questions not provided).	50	10.5
Rosenhall et al. (1999)	Autism	111/57	8 years	Intolerance to broadband CLICKS at 80 dB HL.	18	0
Khalifa et al. (2004)	Autism	11/11	14 years	LDL lower than 80 dB HL.	63	27

Table 2. Prevalence studies on hyperacusis among adults

Author	Country	Method	N	Mean age	Diagnosis based on	Prevalence
Fabijanska et al. (1999)	Poland	Cross-sectional random postal study (on tinnitus)	10,349	Not provided	Not provided	12.5% males 17.6% Females
Rubinstein et al. (1996)	Sweden	Cross-sectional random sample study	1023	38 years	Not provided	23%
Andersson et al. (2001)	Sweden	Cross-sectional Internet study	563	35 years	Positive answer to “Do you consider yourself to be sensitive to everyday sounds?”	9%
		Cross-sectional postal study	584	46 years		8%

did not report discomfort to that highest output of the audiometer were the value of the maximum output with 5 dB added to obtain a more meaningful estimate of the average discomfort level. This most likely underestimates the actual LDLs and we therefore also calculated the 5th percentile the LDL obtained values.

Interview

If a positive answer was given to the question “Are you bothered by any kind of sound or noise?” and the description of this sound and were able to identify at least 10 sounds from a list of 20 sounds asked in the interview as being annoying the responses were classified as being “annoyed by specific sounds.” If a positive answer was given to the question “Are you afraid of sounds?” the participant was classified as having “phonophobia.”

Results

The average LDLs are shown in Table 3. There was a tendency to a gradual increase of the LDLs thresholds toward high frequencies in the range from 0.25 kHz to 6 kHz, followed by a decrease at 8 kHz. The percentage of children where LDLs could not be measured because of the limitations of the output of the audiometer varies according to frequencies being as high as 75% for 8 kHz. Because of that LDLs thresholds for 8 kHz were excluded from analysis.

The flowchart in Fig. 1 outlines the criteria use to classify interview data and to define sound annoyance. Table 4 lists the sounds asked in the interview and the percentage of positive answers given by those children who presented with a score ≥ 10 sounds from the 20 asked in the interview. Table 5 shows the relationships between interview classification criteria and LDLs. Phonophobia was mentioned by 47 (9.3%) of the participants in the whole sample. It was present in 5 (1.2%) in children with hyperacusis.

The characteristics found in the children with hyperacusis compared to the total sample, are listed on Table 6. Moderate to profound hearing loss was present in only one child with hyperacusis but mild to moderate hearing loss was a common finding among them. To evaluate tinnitus we asked “Do you hear a noise inside your ears/head?” and required children to be able to describe the sounds perceived and their location. We refer to this as tinnitus sensation. Those who answered yes to the questions “Does it bother or annoy you?” and “In what situations does it bother or annoy you?” were classified as tinnitus annoyance. Most of the parents had not recognized the symptoms of sound annoyance in their children.

The results of a multivariate logistic regression model (Table 7) show the possible risk factors for occurrence of hyperacusis. All variables listed on Table 6 were included in the model if p -values were < 0.1 . Multicollinearity (variables highly correlated, conveying essentially the same information) was found between self-perception of hearing loss, middle ear disease, and hearing loss. In this

Table 3. Average loudness discomfort levels characteristics ($n = 501$)

Ear	Frequency (kHz)	Maximum (dB HL)	Percentage of subjects with LDLs above the audiometer limits	Mean value (dB HL)	Standard deviation (dB HL)	Median (dB HL)	Minimum (dB HL)	5th Percentile (dB HL)
Right	0.25	> 110	35	106.9	9.9	110	45	85
	0.50	> 120	30	113.1	11.9	115	50	90
	1	> 120	30	114.7	10.3	115	60	95
	2	> 120	30	114.5	10.8	115	60	95
	3	> 120	40	115.6	11.3	120	55	95
	4	> 120	45	116.5	11.3	120	45	95
	6	> 120	55	118.4	10.7	> 120	45	95
	8	> 100	75	102.8	6.1	> 100	45	90
Left	0.25	> 110	35	107.1	9.8	110	50	85
	0.50	> 120	30	112.9	12.1	115	50	90
	1	> 120	35	114.3	11.4	115	50	95
	2	> 120	40	114.6	12.1	120	50	95
	3	> 120	45	115.8	12.2	120	50	95
	4	> 120	50	116.8	11.6	> 120	50	95
	6	> 120	55	117.7	11.6	> 120	45	95
	8	> 100	70	102.4	6.7	> 100	45	90

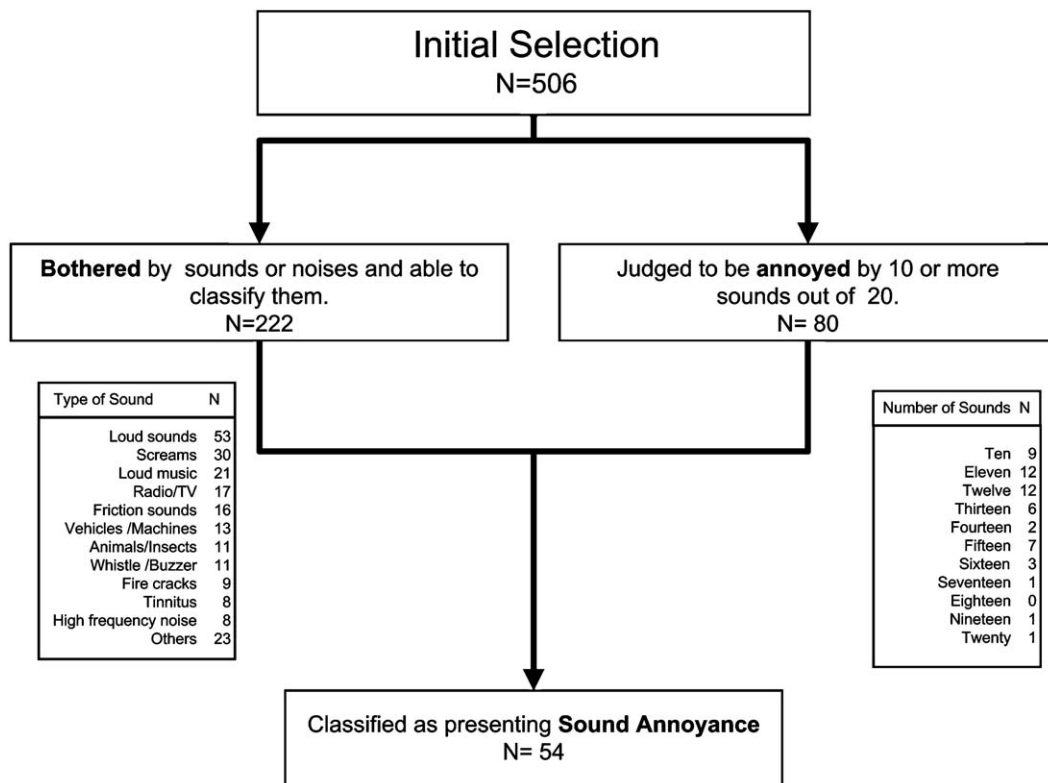


Fig. 1. Classification criteria for interview data on sound reactions.

situation, only one of these three variables could be selected to enter the regression model because it is not possible to include variables that are highly correlated in a regression model and therefore the variable hearing loss was selected. Therefore, minimum mild hearing loss on the left ear was found to be a risk factor for hyperacusis with an Odds Ratio of 3.5 in a Confidence Interval of 1.2–10.8 when compared to normal hearing children.

Discussion

In the present study, hyperacusis was found in 3.2% of the children ($n = 16$). In 5 of these 16 children, phonophobia was a concomitant symptom. Estimates of prevalence of hyperacusis depend on the definitions and the forms of the questions and how the participants' reactions to sounds are described. We have attempted to

separate loudness and annoyance because sounds can be perceived as louder than normal without being annoying; sounds can be annoying without being loud. We are aware that different investigators have used different definitions of the term hyperacusis. Some regard both the elements of louder than normal and annoyance to be included (Tyler, 1999; Tyler et al., 2003), whereas other use the term for describing a lower tolerance to environmental sounds (Baguley, 2003). Sherlock and Formby (2005) observed low LDLs (sometimes around 60–70 dB HL) in normal listeners without sound annoyance complaints.

Loudness discomfort levels

Our definition of hyperacusis includes lowered LDL. We used the threshold value of LDLs at 5th percentile as criteria for hyperacusis because we

could not do a mean value. Children who reported annoyance from sound had significantly lower LDLs than children without complaints. In some cases, 30 children without sound annoyance complaints had LDLs thresholds lower than 70 dB HL. A similar finding was also described by [Sherlock and Formby \(2005\)](#) for adults with normal hearing.

Table 4. Responses only from children who identified 10 or more sounds as being annoying

Sounds asked in the interview: are you annoyed by "..."	Number of children that considered the sound annoying (%) <i>n</i> = 80
TV	21 (26.5%)
Telephone	25 (31.2%)
Toys	26 (32.5%)
Musical instruments	38 (47.5%)
Car	40 (50%)
Dogs	40 (50%)
School bell	43 (53.7%)
Recess	44 (55%)
Ambulance	47 (58.7%)
Balloons	48 (60%)
Motorcycle	49 (61.2%)
Radio	53 (66.2%)
Mixer	54 (67.5%)
Classroom noise	55 (68.7%)
Truck	60 (75%)
Firecracker	64 (80%)
Bombs	64 (80%)
Thunder	66 (82.5%)
Whistle	71 (88.7%)
Screams	73 (91.25%)

The lower limit for normality of LDL thresholds at the 5th percentile were: 90 dB HL at 0.25 kHz; 95 dB HL at 0.5 kHz, and 100 dB HL from 1 kHz to 6 kHz. Similar results were obtained by [Knobel and Sanchez \(2006\)](#) suggesting that the normal range is between 90 and 100 dB HL for young adults and 100 dB HL as suggested by [Sherlock and Formby \(2005\)](#) for adults.

Sound annoyance was reported by 10.5% of the participants in the present study.

Mechanism of hyperacusis

The abnormality expressed as hyperacusis has been regarded to be a compensatory mechanism in acquired hearing loss. [Formby et al. \(2003\)](#) reported that the loudness of warble tones was increased after wearing earplugs for two weeks. These findings were interpreted to support the hypothesis that an auditory gain control process can be modified, in opposite directions by deprivation of sound and by exposure to sounds, a hypothesis first suggested by [Hazell \(1987, p. 98\)](#).

Hyperacusis and tinnitus

[Gabriels \(1996\)](#) in a retrospective study of 21 children with tinnitus complaints, found 33% had decreased tolerance to sound when tinnitus was present. In the present study, 50% of the children

Table 5. Annoyance and loudness discomfort levels including frequencies of 0.25, 0.5, 1, 2, 3, 4, and 6 kHz

	<i>N</i> (%)	LDLs at 5th percentile at least in one frequency in one ear	LDLs at all frequencies < 100 dB HL in the right or in the left ear	LDLs at all frequencies < 90 dB HL on the right or in the left ear	LDLs at all frequencies < 80 dB HL on the right or in the left ear
Total sample	506 (100%)	73 (14.4%)	23 (4.5%)	8 (1.6%)	3 (0.6%)
Are you bothered by sounds? (y/n)	222 (43.5%)	40 (7.9%)	13 (2.6%)	4 (0.8%)	2 (0.4%)
Do sounds on this list annoy you? (identified ≥ 10/20)	80 (15.8%)	22 (4.3%)	9 (1.8%)	5 (1.0%)	3 (0.6%)
Bothered and identified specific annoying sounds	54 (10.7%)	16 (3.2%)	6 (1.2%)	3 (0.6%)	2 (0.4%)

Note: Number in parenthesis represents the percentage of total sample (*n* = 506).

Table 6. Characteristics from the total sample and from children classified as having hyperacusis (criteria: bothered and annoyed by sounds and LDLs in the 5th percentile at least in one frequency at least in one ear)

Variables	Total sample $N = 499$	Hyperacusis $N = 16$
Age		
5 years	27	3
6 years	65	2
7 years	55	2
8 years	58	4
9 years	77	1
10 years	74	1
11 years	93	2
12 years	57	1
Gender		
Male	263	6
Female	236	10
Race		
White	429	15
Black	24	0
Mixed	46	1
Hand writing preference		
Left	51	4
Right	447	12
Both	1	0
School		
Public	412	15
Private	87	1
Parents perception of annoyance to sounds in the subject (parents questionnaire)		
Positive	87	5
Negative	382	9
No answer	30	2
History of ear surgery (parents questionnaire)		
Positive	18	0
Negative	469	16
No answer	12	0
History of otitis on the last 12 months (parents questionnaire)		
Positive	95	6
Negative	374	10
No answer	30	0
History of noise exposure		
Positive	95	5
Negative	393	11
No answer	11	0
Middle ear evaluation (otoscopy)		
Normal	419	12
Altered	80	4
Vestibular symptoms		
Positive	108	5
Negative	183	3
Not diagnosed	208	8
Motion sickness		
Positive	206	9
Negative	293	7
Self perception of hearing		
Normal	96	7
Altered	403	9

Table 6. (continued)

Variables	Total sample $N = 499$	Hyperacusis $N = 16$
Audiometric evaluation right ear		
Normal	431	12
Minimal/mild hearing loss	58	4
Moderate/profound hearing loss	10	0
Audiometric evaluation left ear		
Normal	426	10
Minimal/mild hearing loss	61	5
Moderate/profound hearing loss	12	1
Audiometric evaluation both ears		
Normal	408	10
Minimal/mild hearing loss	72	5
Moderate/profound hearing loss	19	1
Tinnitus suffering		
Positive	96	8
Negative	384	8

Table 7. Risk factors for hyperacusis on a multivariate regression model analysis

Variables	Hyperacusis odds ratio (95% confidence interval)
Audiometric evaluation left ear	
Normal	Reference
Minimum/mild hearing loss	3.5 (1.2–10.8)
Moderate/profound hearing loss	3.4 (0.4–3.0)
Audiometric evaluation	
Normal	Reference
Minimum/mild hearing loss	–
Moderate/profound hearing loss	–

who had hyperacusis also reported tinnitus. Of those children who did not have hyperacusis, 17.8% reported tinnitus. A link between hyperacusis and tinnitus has been described a long time ago (Tyler and Conrad-Armes, 1983). Estimates of the prevalence of hyperacusis in individuals with tinnitus range from 40% (Coles and Sood, 1988; Fabijanska et al., 1999; Jastreboff and Jastreboff, 2000) to 60% (Andersson et al., 2001). Anari et al. (1999) reported that 86% of the participants in their study with hyperacusis also had tinnitus. However, we believe this is the first demonstration of such link in a randomly selected and controlled sample.

Conclusion

Tinnitus is frequently a concomitant symptom to hyperacusis that affects children. As for tinnitus

the results of studies of the prevalence of hyperacusis depend on which definition of hyperacusis is used.

Acknowledgments

This study was partially supported by a grant from the Fundação de Amparo à Pesquisa de São Paulo (Fapesp 03/00574-5). We are grateful to Jacqui Sheldrake for important suggestions made on the interview protocol; Sandra Weber, responsible for all the audiometric evaluations; Keila Knobel and Matt Gilchrist, who provided helpful comments regarding earlier versions of this manuscript. Statistical analyses done by Ana Capuano were much appreciated.

Appendix 1: Parent's questionnaire

Do you think that your child is too sensitive to every day's sounds?
 Is there any sound that your child dislikes?
 Is there any sound that your child considers painful?
 Is there any sound that is annoying you?
 Does your child use any medication?
 Has your child been submitted to ear surgery?
 How many ears infections has your child had in the last 12 months?

Appendix 2: Children's interview

Can you hear well?
 Are you bothered by any kind of sound or noise? How does it sound like?
 Do any of the following sounds annoy you?

Recess	TV	Car	Toys	Firecrackers
Classroom noise	Radio	Motorcycle	Balloons	Bombs
Screams	Mixer	Truck	Whistle	Thunder
School bell	Telephone	Ambulance	Musical instruments	Dogs

Have you ever been exposed to loud sounds or explosions? What kind? When
 Do you hear a noise inside your ears or head?
 Where do you hear it?
 What does it sound like?
 Does it bother or annoy you?
 Do you feel dizzy or have nausea while playing in the playground?
 Do you feel nausea, dizziness or headache when you ride a car or a bus?
 Do you feel dizzy?

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CHAPTER 16

Tinnitus in children and associated risk factors

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Abstract: The objective of the study was to estimate the prevalence of tinnitus and explore the risk factors in school-aged children age 5–12 years. For that we asked “Do you hear a noise inside your ears/head?” and required children to be able to describe the sounds perceived and their location. We refer to this as tinnitus sensation. Additionally, we asked “Does it bother or annoy you?” and “In what situations does it bother or annoy you?” to determine if this experience was bothersome. We refer to this as tinnitus annoyance. Associations to demographic and audiological factors were studied. Approximately 37% of children reported tinnitus sensation and 17% reported tinnitus annoyance. Related factors were age, hearing loss, and history of noise exposure, motion sickness and hyperacusis. Estimates of the prevalence of tinnitus clearly depend on how tinnitus is defined. In the present study, participants were asked “Do you hear a noise inside your ears/head?” but we did not make distinctions regarding the duration or character of their tinnitus. Our estimates of tinnitus annoyance were also broad, and did not attempt to quantify the degree of annoyance.

Keywords: tinnitus; hyperacusis; children; cross-sectional study; prevalence

Introduction

Children experience tinnitus as frequently as adults, but most of them do not seem to be bothered. In some cases, they might present similar suffering as observed in adults (Martin and Snashall, 1994). Tinnitus can cause a significant influence on children’s life which will inevitably affect their families as well (Kentish and Crocker, 2006).

Investigating tinnitus in childhood is challenging because of its subjectivity and because children are different from adults in several ways. Mills et al. (1986) suggested that statistics in children are

underestimated due to communication difficulties. Conversely, Stouffer et al. (1991) argued that children have a tendency to over-report tinnitus when inquired to please the questioner. The rate with which children seek professional help might not reveal the true prevalence because children rarely report tinnitus spontaneously (Fowler and Fowler, 1955; Graham, 1965) and presence of tinnitus is seldom an item in routine pediatric otolaryngological examinations.

Population studies on the epidemiology of tinnitus among children have disclosed prevalence rates from 6% to 59% (Table 1). These studies have differed significantly in their methods of data collection, diagnostic criteria, and age groups.

An effort to minimize communicating problems with children was done by Stouffer et al. (1991)

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Table 1. Epidemiological studies on tinnitus among children in general population

Author	Place	N	Age	Diagnosis based on	Prevalence	
Nodar (1972)	USA	2000	10–18	Questionnaire “Do you hear a noise in your ears like ringing, buzzing, or a click?”	13.3% normal hearing	58.6% hearing impaired
Stouffer et al. (1991)	Canada	161	7–12	Interview “Do you hear a noise in your head for more than 5 minutes?”	13% in normal hearing 6% after an answer (consistency criteria)	29% in hearing impaired 24% after an answer (consistency criteria)
Holgers (2003)	Sweden	964	7	Questionnaire (a) “After listening to loud music or other loud sounds/ noise, have you afterwards heard a ringing, buzzing or other sort of noise in your ears, even if the loud music or noise has been turned off?” (b) “Have you heard a ringing, ... ears, without first having listened to loud music or other loud sounds?”	13% in normal hearing	8.8% in hearing impaired
Holgers and Pettersson (2005)	Sweden	671	13–16	Questionnaire (a) “How often do you experience tinnitus?” (b) “How often is tinnitus annoying?” (c) “Thoughts about tinnitus”	53% tinnitus perception	27% tinnitus annoyance
Aksoy et al. (2007)	Turkey	1020	6–16	Questionnaire (a) “Have you ever had noises in your head or ears?” (b) “Nowadays do you hear noises in your head or ears?”	9.2% tinnitus perception	5.8% tinnitus annoyance

who used a questionnaire with different approaches to the same questions to verify the responses. The results of epidemiologic studies of tinnitus among children also depended on how rigorously the examiners applied their criteria (Table 1). Assessing the difference between the perception of a sound, (tinnitus sensation) and the impact of tinnitus on a person (tinnitus suffering) provides information about the prevalence of problematic tinnitus; but that was rarely adopted in the published studies of tinnitus in children (Table 1).

The purposes of present study were (1) to determine the prevalence of tinnitus in a general pediatric population, differentiating sensation from suffering and (2) to determine the importance of risk factors such as noise exposure, history of otitis media, otologic surgery, middle ear alterations, and hyperacusis.

Methods

A prospective cross-sectional study of the presence of tinnitus among 13,000 children of the public and private elementary schools in Lajeado, a southern Brazilian town of 64,133 inhabitants was done between September 2002 and December 2003.

Selection criteria

Among the 13,000 children, 700 children 5–12 years of age were randomly selected, 516 of the children's parents (75%) returned the informed consent. Ten of them were excluded for the following reasons: fear of performing the evaluation ($n = 4$) and incomplete examination dates after three attempts ($n = 6$). The final sample included 506 children.

Procedure

This sample was selected on a two-stage cluster sampling (Abramson, 2002). The primary units (clusters) were the 44 schools. The sampling frame was all the schools in the town, from which schools were selected using probability proportional to school size. Each school on the list was allocated a weighting equivalent to the number of children enrolled who were eligible to be selected for the study. The proportion of children in public to private schools was 4:1. Therefore, 75% of the sample was taken from public schools. The secondary (the second cluster were children at school) units were the children in the schools. Equal numbers of children between 5 and 12 years were sampled from each school. Children in the schools were allocated code numbers and then randomly selected. Two weeks before the physical examination, the school distributed to the parents an explanatory letter, a questionnaire to be filled out at home, and the informed consent letter. One week later, the teachers collected the returned letters.

Data collection and design

The present study was approved by the ethics committee of research of the University of São Paulo. Written consent was obtained from all parents and verbal consent from all children. The data were collected in a cross-sectional survey. Questionnaire data were collected from parents, and the interviews were conducted with the children, as well as the otoscopic evaluation and hearing tests. All children were interviewed and examined by the first author and all audiometric tests were performed by the same audiologist in a standardized manner. Care was taken to ensure that the children understood the questions. They were given ample time to respond.

The parents' questionnaire sought information on parental impressions of their own and their children's experience of annoyance from sound, as well as on their use of medication, number of episodes of otitis media in the last 12 months and any ear surgeries. The first author conducted these

interviews after a pilot study that included 46 children.

Wax or debris was present in the external auditory meatus and removed after otoscopic examination in 80 (16%) of 504 children. The tympanic membranes were evaluated concerning position, aspect, integrity, and other occasional findings.

Hearing tests included air conduction audiometry (interacoustics audiometer, model AD28, ear phone model TDH-39), tympanometry, and contralateral acoustic reflex threshold (Rexton-Danplex immittance device), performed in a portable acoustic booth (Vibrasom, model VSA40). The audiometer and immittance device were calibrated according to the American National Standard Institute (ANSI) 3.6-1996. Pure-tone thresholds were at octave frequencies from 0.25 kHz to 8 kHz, and at the half-octave frequencies 3 and 6 kHz. Hearing thresholds were determined according to ISO 8253-1 using a modified Hughson-Westlake procedure (ISO 8253-1, 1989). When air conduction thresholds were >15 dB HL, bone conduction thresholds were obtained at 0.5, 1, 2, 3, and 4 kHz. Loudness discomfort levels (LDL) were determined at octave frequencies from 0.25 kHz to 8 kHz, half-octave frequencies 3 and 6 kHz. The quality of the response depends on how the instructions were worded (Beattie et al., 1979; Bornstein and Musiek, 1993). We used a modified version of the instructions proposed by Hawkins (1980). Before the measurements the participants received the following instructions: "You are going to hear a noise that will become louder and louder. When the noise is too strong and you don't want to hear it anymore, raise your hand and the sound will stop immediately." After that the children's discomfort level was determined. Pulsed tones were presented for 2 s with an interval of 1 s before each increment on the following sequence: 1; 2; 3; 4; 6; 8; 0.5; and 0.25 kHz. The initial stimuli were presented at 50 dB HL, increased by 5 dB until the child raised the hand or demonstrated discomfort. Right ear was tested first. After testing the left ear, both ears were tested again in the same way as before. Threshold values used were those from the retest.

Data analysis

Two pure-tone average (PTA) scores were calculated for each ear one for low frequencies (0.5, 1, and 2 kHz) and one for the high frequencies (3 and 4 kHz). Mean values of both PTAs were used to classify the degree of hearing loss according to [Silman and Silverman \(1997\)](#): normal hearing, 10–15 dB HL; (b) minimum loss, 16–25 dB; (c) mild, 26 dB HL; (d) moderate loss, 41–55 dB HL; (e) moderate to severe loss, 56–70 dB HL; (f) severe loss, 71–90 dB HL; and (g) profound loss, >91 dB HL.

No data on LDL is available for children and therefore no normal range has been established. In a pilot study we found that many children did not report discomfort even at the maximum output of the audiometer. This limits the use of mean value and standard deviation for LDL and we therefore used the 5th percentile as a cut off level abnormal LDL.

When a positive response to the question “Do you hear a noise inside your ears/head?” children had to be able to describe, “Where do you hear it?” and “What does it sound like?” in order that the response was regarded to be positive. The children who gave a positive answer to the question “Does it bother or annoy you?” were classified as having tinnitus sensation if they could answer the question “In what situations does it bother or annoy you?”

Four electronic questionnaires were designed to collect 140 variables for this study: Parental information, children’s interview, otoscopic examination and audiological evaluation. Tables were precoded with normalized data (e.g., school names) to guarantee uniformity. This information composes the individual file of every participating child. These files were directly stored on the databank and information was automatically entered into the databank to reduce manual data entry problems.

Statistical analysis

Statistical analysis of the collected data were performed by a professional statistician using SAS

(version 9.1, SAS Institute, Inc., Cary, NC) software. Chi-square or two-sided Fisher’s exact test were used to access bivariate risk factor associations and demographics, as well as symptoms. Unconditional logistic regression was used to examine multiple independent variables for their association with the outcomes. Final multivariate models were designed using a saturated model and manual backwards elimination. Covariates with bivariate *P*-values <0.1 were considered for inclusion in all logistic regression models, while multicollinearity was checked. Logit (estimated log odds) plots with the continuous variables were used to check linearity. Ninety-five percent confidence intervals were computed around adjusted odds ratio.

Results

There were 240 girls (47.4%) and 266 boys (52.6%), mean age 9.46 (SD = 2.09) in the study; 86.2% white, 9.1% mixed, and 4.7% black. Hearing thresholds were classified as normal in 81% (*n* = 411), minimum to mild loss in 14% (*n* = 72), and moderate to profound hearing loss in 4% (*n* = 19) of the children.

Tinnitus sensation was confirmed in 37.5% of the children (*n* = 190) and tinnitus suffering in 19.6% (*n* = 99). The classification criteria are described in [Fig. 1](#). Tinnitus characteristics, location, and situations of annoyance are also described.

[Table 2](#) lists the characteristics of the children who were classified as having “tinnitus sensation” and those who were classified as having “tinnitus suffering.” Children who did not meet the classification criteria for tinnitus sensation (*n* = 19) and tinnitus suffering (*n* = 21) were excluded from further analysis.

Children who related exposure to noise and were able to describe the source were classified as having a positive history of noise exposure. Normal self-perception of hearing was classified in case of positive answer to the question “Can you hear well?” showing to be a common finding among children with tinnitus. Results regarding hyperacusis are described in Chapter 15. A

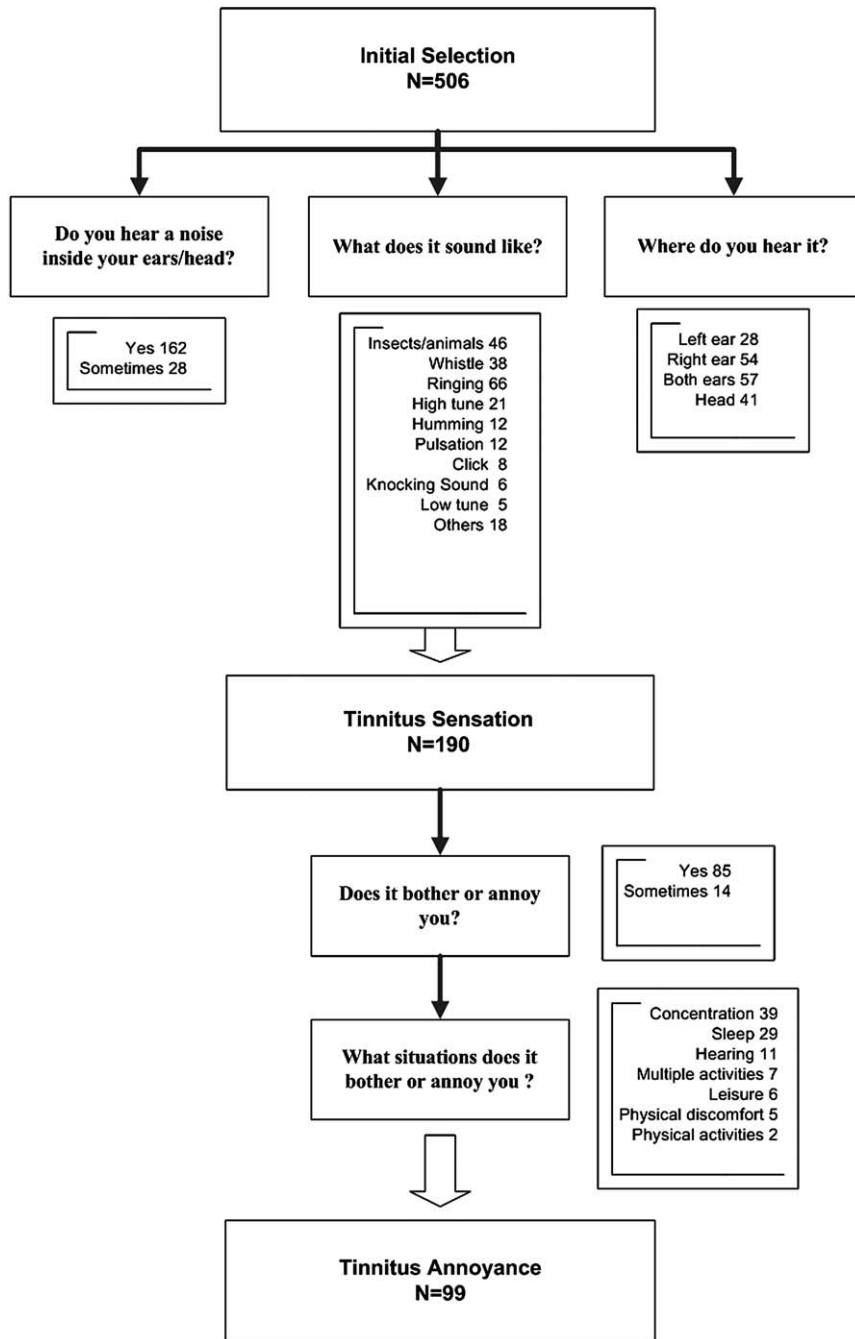


Fig. 1. Criteria steps on tinnitus classification.

Table 2. Sample characteristics according to the presence of tinnitus

Variable	Tinnitus sensation		Tinnitus suffering	
	Total sample (<i>N</i> = 487)	Positive (<i>N</i> = 190)	Total sample (<i>N</i> = 485)	Positive (<i>N</i> = 99)
Age				
5	4	1	4	1
6	53	10	53	5
7	53	26	47	14
8	54	17	55	6
9	68	27	68	12
10	75	26	75	10
11	81	39	80	22
12	99	44	103	29
Gender				
Male	258	93	255	40
Female	229	97	230	59
Race				
White	419	165	421	88
Black	24	11	23	6
Mixed	44	14	41	5
Hand preference for writing				
Left	49	25	47	14
Right	437	165	437	85
Ambidextrous	1	0	1	0
Type of school				
Public	401	163	401	86
Private	86	27	84	13
History of noise exposure				
Positive	93	47	94	33
Negative	384	137	381	62
No answer	10	6	10	4
History of otitis on last 12 months (parental information)				
Positive	94	36	92	25
Negative	367	141	367	66
No answer	26	13	26	8
Middle ear disease				
None	409	154	407	79
Present	77	36	77	20
History of ear surgery (parental information)				
Positive	16	9	16	4
Negative	460	174	459	91
No answer	11	7	10	4
Prevalence of vestibular symptoms				
Positive	106	58	107	35
Negative	183	55	179	22
Not classified	198	77	199	42
Prevalence of motion sickness				
Present	202	95	195	48
Absent	285	95	290	51
Self-perception of hearing loss				
Positive	94	57	92	40
Negative	393	133	393	59
Hearing loss — right ear				
Normal	420	157	417	77
Minimum/mild	54	29	56	19

Table 2 (continued)

Variable	Tinnitus sensation		Tinnitus suffering	
	Total sample (<i>N</i> = 487)	Positive (<i>N</i> = 190)	Total sample (<i>N</i> = 485)	Positive (<i>N</i> = 99)
Moderate/profound	9	2	8	1
No answer	4	2	4	2
Hearing loss — left ear				
Normal	415	160	411	75
Minimum/mild	57	25	60	20
Moderate/profound	11	3	10	2
No answer	4	2	4	2
Hearing loss — both ears				
Normal	398	150	394	70
Minimum/mild	68	34	71	24
Moderate/profound	17	4	16	3
No answer	4	2	4	2
Hyperacusis				
Present	16	8	16	8
Negative	466	179	464	88

Note: Sample characteristics according to the presence of tinnitus sensation or suffering.

Table 3. Risk factors for tinnitus sensation and tinnitus suffering on a multivariate regression model

Variable	Tinnitus sensation OR (95% CI)	Tinnitus suffering OR (95% CI)
Age (continuum)	1.1 (1.06–1.3)	1.2 (1.1–1.4)
Gender (male vs. female)	–	0.5 (0.3–0.9)
Hearing loss		
Normal	Reference value	Reference value
Minimum/mild	1.8 (1.05–3)	2.4 (1.4–4.4)
Moderate/profound	0.5 (0.2–1.6)	1.1 (0.3–4.1)
History of noise exposure (positive vs. negative)	1.8 (1.1–2.9)	2.8 (1.6–4.8)
Motion sickness (positive vs. negative)	1.8 (1.3–2.7)	–
Hyperacusis (positive vs. negative)	–	4.2 (1.4–12.6)

multivariate logistic regression model (see Table 3) was created to evaluate possible risk factors for occurrence of the tinnitus that was classified as “tinnitus sensation” and “tinnitus suffering.” All variables listed on Table 2 were considered to this model if *P*-values were <0.1. Multicollinearity (multiple regressions in which the predictor variables are themselves highly correlated) was found among self-perception of hearing loss, middle ear disease, and hearing loss. Since only one of these three variables could be selected to enter the regression model, the variable hearing loss was chosen. According to the statistician, I had to choose between one of these three variables, since only one could enter the regression model. I opted for

hearing loss; Minimum mild hearing loss was found to be a risk factor for “tinnitus sensation” and “tinnitus suffering” with an odds ratio of 1.8 and 2.4 in a confidence interval of (1.05–3) and (1.4–4.44), respectively, when compared to normal hearing children. Age, being a female, positive history of noise exposure, motion sickness, and hyperacusis were also found to be risk factors for tinnitus (Fig. 2).

Discussion

When studying tinnitus among children, it should be kept in mind that a child is not a small adult.

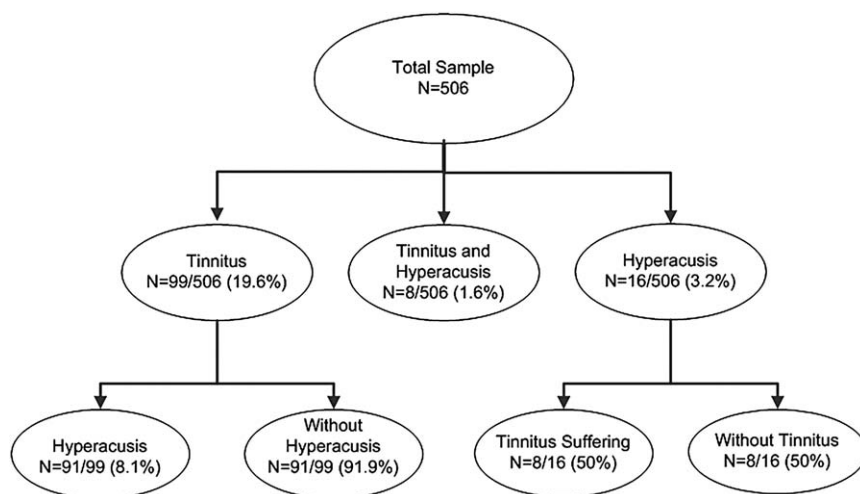


Fig. 2. Tinnitus and hyperacusis frequencies on the sample.

For example, it has been shown that somatosensory stimulation can change loudness perception in children but that is less likely in adults (Møller and Rollins, 2002) indicating that the nonclassical (extralemniscal) auditory pathways (Møller, 2003) are commonly active in children but rarely in adults. Their auditory pathway and neural connections is under a maturation process (Werner, 1996) and is expected to be more plastic and therefore more likely to be influenced by external influence such as noise and biochemicals. Children react to tinnitus differently from adults, manifesting the symptom in distinct ways. Also, the progressive risk for tinnitus associated with age could be related to an increase in cognitive capacity or because of an accumulative exposure to many factors implicated in tinnitus etiology as noise exposure.

Prevalence

In this study of children in the age range of 5–12 years the general over all prevalence of tinnitus was 37.5% ($n = 190$) for sensation and 19.6% ($n = 99$) for suffering. Mills et al. (1986) were the first to report prevalence of tinnitus in children using this classification. They found tinnitus sensation in 29% of the sample and suffering in 9.6% among 93 children with age range from 5 to 16

years in a nonrandomized sample. Holgers and Pettersson (2005) showed prevalence for tinnitus perception in 53% ($n = 356$) and tinnitus annoyance in 27% ($n = 185$) of children age 13–16 years. Aksoy et al. (2007) found a prevalence of 9.2% ($n = 94$) of tinnitus that was not regarded to be bothering and 5.8% ($n = 60$) of tinnitus disturbance in a sample of 1020 children and adolescents from 6 to 16 years of age. We found prevalence of tinnitus that was in the middle of the range of the prevalence rates of the two first mentioned studies.

In the present study, children classified as having normal hearing thresholds, “tinnitus sensation” occurred in 37.7% ($n = 150$) and suffering occurred in 17.8% ($n = 70$), respectively. The prevalence described in other studies was lower and varied from 13% (Nodar, 1972; Holgers, 2003) to 6% (Stouffer et al., 1991).

In children with hearing loss, “tinnitus sensation” occurred in 50% of the children ($n = 34$) who had minimum to mild hearing loss and in 23.5% ($n = 4$) in moderate to profound hearing loss. Suffering was classified in 33.8% of the children ($n = 24$) with minimum to mild hearing loss and in 18.8% ($n = 3$) with moderate to profound hearing loss. Nodar (1972) described a prevalence of tinnitus in 58.6%, Stouffer et al. (1991) in 29%, and Holgers (2003) in 9%. Our finding is similar to published reports regarding children with hearing deficiency, where it was shown that tinnitus is

more prevalent the milder the hearing loss is (Graham, 1981b; Nodar and Lezak, 1984).

The variation in the reported prevalence of tinnitus in the different population studies may be explained by different definitions of tinnitus, the age range of the participants in the studies that varied from 10 to 18 years (Nodar, 1972), 7 to 10 years (Stouffer et al., 1991), and 7 years (Holgers, 2003). Difference in methodology and classification of audiometric results are different between studies and that may have contributed to the differences in the obtained results.

Only eight children (1.6%) mentioned. Without being directly asked about tinnitus, the question was: are you bothered by any sound? I was asking about external sounds, but they mentioned spontaneously that they had tinnitus. This finding considers our attention because when directly asked about the perception of tinnitus, approximately 1/3 of all children studied gave a positive response. Similar results are described by Nodar and Lezak (1984) and Mills et al. (1986) who reported spontaneous complaints in 3% of the children. These data support Fowler's (Fowler and Fowler, 1955) and Graham's (1965) statement that children rarely complain about tinnitus.

Many hypotheses have been presented regarding why children do not spontaneously report that they have tinnitus. One reason may be that children rarely refer to symptoms that are not associated to pain (Graham, 1965), or that children have a less developed body image (Leonard et al., 1983). Children may perceive tinnitus as a familiar experience (Mills and Cherry, 1984). Children may be more easily distracted by external environments (Viani, 1989) or do not perceive the medical significance of the symptom (Savastano, 2002). Because children will rarely mention tinnitus, the only way to investigate the symptom and possible effects on life is directly asking. Although, care must be taken in the approach, since children tend to give positive answers to please the interviewer (Stouffer et al., 1991). It is equally important to minimize the possible preoccupations that children and parents might have after being conscious about tinnitus.

The degree of tinnitus annoyance is difficult to evaluate, as already described by Graham (1965).

There are no instruments developed to investigate annoyance among children, for example, no questionnaire or visual-analog scales are validated to study tinnitus in the pediatric population. Difficulty in concentration (33%), sleeping (24%), and hearing (9%) were the most frequent complaints from the children in the present study. They also related interference in leisure, sports and the symptom was associated to headache and dizziness. Similar findings among children were described by Martin and Snashall (1994), Gabriels (1996), and Aksoy et al. (2007). Decrease in school performance was related by Druker (1989) and Kentish et al. (2000). All these findings were similar to those related by adults who seek help for their tinnitus in Brazil (Coelho et al., 2004).

Since tinnitus' definition is not uniform (Davis and El-Rafaie, 2000) and prevalence studies among adults also vary given differences in the definition of tinnitus and methodology it is difficult to compare the prevalence of tinnitus in children and adults. Most epidemiological studies base their definition of tinnitus on an experience perceived for more than 5 min. Tinnitus' prevalence rates vary from 25% to 44% (Leske, 1981); 29% (Hinchcliffe, 1961); 14.2% (Axelsson and Ringdahl, 1989) to 10% (Heller and Bergman, 1953). In a historical experiment about tinnitus sensation, Heller and Bergman (1953) reported that 94% of participants who entered in a sound proof booth reported some form of tinnitus. This finding was confirmed by Graham and Newby (1962) who reported similar experience in 40% of individuals with normal hearing participants. Besides methodology and definition differences, the discrepant prevalence found in this pediatric population when compared to adults might also reflect differences in behavior and maturation of the auditory pathway.

Risk factors associated with tinnitus sensation and suffering

The risk for tinnitus sensation and tinnitus annoyance has been shown to be progressive as age increases with a risk of 1.1 and 1.2 times, respectively for every year raise. Nodar (1972) in a

sample from 10 to 18 years and Aksoy et al. (2007) 6 to 16 years, observed a progressive increase in tinnitus incidence until 13 to 14 years of age in their studies. This tendency was confirmed in the present study, but we could not verify if the prevalence kept increasing until 14 years because our age limit was 12 years of age.

The prevalence of tinnitus in adults varies with age. Among young adults (18–24 years of age), Hinchcliffe (1961) and Leske (1981) described tinnitus prevalence in 21% and 26.6%, respectively. A progressive prevalence of tinnitus, proportional to age is followed by a decline after a plateau around 65 years of age (Hoffman and Reed, 2004).

Gender

Most epidemiological studies among adults show similarity between genders or a small increase in women when compared to men. Nondhal et al. (2002) using a logistic multivariate model have demonstrated an odds ratio of 1.3 (95% IC 1.06–1.08) of higher risk among women. In our study, boys had an odds ratio of 0.5 (95% IC 0.3–0.9) to present tinnitus suffering when compared to girls, meaning that male gender was a protective factor for the development of tinnitus among children. Holgers and Svedlund (2003) have described a higher prevalence of tinnitus among girls, as well as a higher prevalence of depressive and anxiety symptoms. This could be related to: (a) girls present a higher tendency to express symptoms than boys, including those related to affective disorders (Eley et al., 1999); (b) spontaneous otoacoustic emissions, which have been described as a possible tinnitus etiology (Penner, 1992), are more frequent among females (Burns et al., 1992); (c) genetic differences among genders associated to neurotransmitters expressions pursuing an action on auditory pathway, including serotonin (Weiss et al., 2005).

Hearing loss

The prevalence of tinnitus in children with hearing loss has shown to be greater than that in normally hearing children. The present study showed that

tinnitus was less prevalent in children with moderate to profound sensory-neural hearing loss, than in those children with minimum to mild hearing loss. Minimum to mild hearing loss was found to be a risk factor for tinnitus with an odds ratio of 1.8 for tinnitus sensation and 2.4 for tinnitus suffering. Moderate hearing loss to profound hearing loss (deafness) was also considered risk factors with an odds ratio of 0.5 and 1.1 for tinnitus sensation and tinnitus suffering, respectively. These results are in agreement with earlier studies where it was found that the prevalence of tinnitus is smaller among children with normal hearing (Nodar, 1972; Stouffer et al., 1991) than among hearing impaired children. Tinnitus is less frequent among those with severe hearing loss whereas with profound hearing loss have been found to have lower prevalence of tinnitus than children with moderate loss (Graham, 1981a). In a study comparing the prevalence of tinnitus children with middle ear disease and sensorineural hearing loss it was found that 43.9% of children with middle ear disease had tinnitus while only 29.5% of those with sensorineural hearing loss had tinnitus (Mills and Cherry, 1984). All these findings are in agreement with those of the present study.

The finding that mild hearing loss is a risk factor for tinnitus in children may be explained by the finding that even a mild hearing loss (thresholds <30 dB HL) could promote tonotopic reorganization of the auditory cortex (Norena and Eggermont 2005) (see Chapters 2 and 3).

Noise exposure

Exposure to impulse noise has been significantly associated to tinnitus in uni- and multivariate regressions models (Hoffman and Reed, 2004). A similar finding among children has recently been related by Holgers and Petterson (2005), who found exposure to sounds in concerts and discos to be associated to tinnitus sensation, in a multivariate regression model. The present study confirmed that a history of noise exposure was a risk factor for both tinnitus sensation and tinnitus suffering with odds ratio of 1.8 (IC 95% = 1.1–2.9) and 2.8 (IC 95% = 1.6–4.8), respectively.

Segal et al. (2003) reported that 25% of children ($n = 13$) who searched for medical care after being exposed to noise from toys and firecrackers. In our study, the most frequent occurrence of noise exposure was related to firecrackers that might produce noise with peak levels of 145–165 dB HL at a distance of 2 m or less from the explosion site (Smootenburg, 1993). The risk of frequent exposure to excessive noise from toys has also been mentioned by Axelsson et al. (1984) and Rytzner and Rytzner (1981).

Reorganization on the tonotopic map of the primary auditory cortex following noise trauma has been documented in several studies (Robertson and Irvine, 1989; Komiya and Eggermont, 2000) and has been suggested to cause tinnitus (Rauschecker, 1999; Norena et al., 2002; Norena and Eggermont, 2003).

Motion sickness

Motion sickness has been shown to be a risk factor for tinnitus sensation in our study, with an odds ratio of 1.8 (CI 95% = 1.3–2.7). Motion sickness has been demonstrated to be highly associated to migraine and vestibular symptoms in children (Uneri and Turkdogan, 2003). Recently, Neuhauser et al. (2005) found a strong association of vestibular vertigo with tinnitus in adults but we could not find similar data in children.

Hyperacusis

Hyperacusis and tinnitus have been well described as related symptoms (Tyler and Conrad-Armes, 1983). In our study, the presence of hyperacusis demonstrated to be the highest risk factor for tinnitus suffering, with an odds ratio of 4.2 (CI 95% 1.4–12.6). On the other hand, the presence of tinnitus does not appear to be a risk factor to hyperacusis (Chapter 15).

Conclusion

Tinnitus sensation is a common finding among children. In some cases it might cause interference in concentration, sleeping, and hearing and

become a problematic symptom. Because children often do not complain about tinnitus, it is likely to be unnoticed by parents and clinicians. Differences in prevalence rates among studies between children can be attributed to different methodologies, questionnaires, and the way tinnitus is defined. Appropriated instruments to evaluate tinnitus annoyance in childhood still have to be validated and are necessary to classify the degree of distressing of this symptom among children to determine possible therapeutic effects of intervention and maturation in this population. A definition of tinnitus in children is fundamental to create a unified protocol for future epidemiological studies. Comparison between tinnitus in adults and children indicate that differences in their auditory systems may account for some of the differences and children may be more susceptible to agents causing tinnitus.

The role of nonclassical (extralemniscal) auditory pathways and its influence on tinnitus perception and suffering from tinnitus among children should be addressed in futures studies. Children should be counseled, probably in schools (initiated in early years) and in high-risk activities, that high noise levels should be limited (by avoidance, limiting the time of exposure and/or using hearing protection) to avoid tinnitus and hearing loss.

Acknowledgments

This study was partially supported by grants from the Fundação de Amparo à Pesquisa de São Paulo (Fapesp 03/00574-5). We are grateful to Sandra Weber, who was responsible for all audiometric evaluations of the children in the study; and Keila Knobel and Matt Gilchrist, who provided very helpful comments on earlier versions of the manuscript. Statistical analysis performed by Ana Capuano was much appreciated.

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CHAPTER 17

Evidence for a tinnitus subgroup responsive to somatosensory based treatment modalities

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Abstract: Studies have established that the somatosensory system of the upper cervical region and head can be intimately involved in tinnitus. Tinnitus can arise directly from a disorder of the head and upper neck through activation of the somatosensory system. “Somatic testing” (a series of strong muscle contractions of the head and neck) can (1) modulate the tinnitus percept of ~80% of people with ongoing tinnitus, and (2) elicit a sound percept in ~50% of people with no tinnitus. These somatic phenomena are equally prevalent among people with or without functioning cochlea. Likely neural pathways underlying both the induction and modulation of tinnitus have been revealed in animal studies. Because somatic influences are fundamental to the operation of the auditory system, in general, and to tinnitus, in particular, somatic testing should be incorporated into all evaluations of tinnitus (1) to improve understanding of the role of the somatosensory system in any individual and (2) to identify subgroups of tinnitus patients who may respond to a particular treatment modality (as has already been shown for the tinnitus associated with temporomandibular disorder). Our clinical experience and review of reports of treatment modalities directed toward the somatosensory system supports the hypothesis that these modalities can benefit individuals with symmetric hearing thresholds but asymmetric widely fluctuating tinnitus. Treatment modalities involving the somatosensory system should be re-assessed by targeting this tinnitus subgroup.

Keywords: acupuncture; trigger point injections; temporomandibular; dorsal cochlear nucleus; electrical

Introduction

As a symptom and not a disease, tinnitus has many causes (see Chapter 1). The most common neurological system associated with the abnormal auditory perception known as tinnitus is, of course, the auditory system. However, an experienced clinician once observed, “If the probability is assessed

as being over 50% that a particular condition is causing the tinnitus, ... most cases of tinnitus would have to be classified as ‘unknown’” (i.e., idiopathic) (Coles, 1996). His statement implies that a disordered ear or auditory nerve cannot be implicated as causing tinnitus with a high level of certainty in the majority of people. On the other hand there is evidence for an association between the degree of hearing loss and the likelihood of developing tinnitus. This fact can be deduced from two well-established facts regarding tinnitus’ prevalence: (a) in adults with no hearing impairment

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~10% report tinnitus (Levine et al., 2003) and (b) in adults with profound hearing loss ~80% report tinnitus (Chung et al., 1984; Levine, 1999) (see Chapter 1). Yet, frequently hearing loss per se cannot be implicated as the immediate precipitant or “trigger factor” for tinnitus onset in either of these populations. A typical example is as follows.

Case 1. A 57-year-old man reported 4 months of constant ringing or roaring tinnitus in both ears. He reported no associated symptoms with the tinnitus onset; in particular he had no dizziness, change in his hearing, or ear pressure. He denied trauma, recent dental work, or change in medications at or near the time of his tinnitus onset. An audiogram following his tinnitus onset was unchanged as compared to one from 2 years earlier. Pure tone thresholds were symmetric. He had normal hearing thresholds at 1 kHz and below. Above 1 kHz thresholds were progressively increasing reaching 45 dB HL at 8 kHz. Speech discrimination scores were normal. His otoneurological examination was unremarkable.

While in this case a symmetric mild hearing loss was present, with his tinnitus onset no other hearing or vestibular symptom were noted by the patient and his audiogram was unchanged. On the one hand, his hearing loss would appear to be a risk factor for his development of tinnitus. On the other hand, the cause for its onset 4 months prior to our evaluation could not be determined. Only when hearing loss and tinnitus develop acutely together can the two be considered causally related.

The somatosensory system and tinnitus

Of all the sensory systems other than auditory, only the somatosensory system has been shown to be closely related to tinnitus. Observations abound supporting the notion that head and neck somatic events can be associated with tinnitus (Levine, 1999). Tinnitus is generally included among the features associated with discomfort in the temporal or preauricular region that goes by various names such as Costen’s syndrome,

craniomandibular disorder, temporomandibular joint syndrome, or temporomandibular disorder (TMD). Studies have shown a higher incidence of tinnitus in individuals with normal hearing who have TMD as compared to controls (Chole and Parker, 1992). The same is true regarding the whiplash syndrome, where the association has been attributed to “functional disturbances of the upper cervical spine” (Tjell et al., 1999). From multiple other observations and case reports the concept of tinnitus associated with whiplash and TMD can be generalized to include tinnitus associated with any disorder of the upper cervical region and head, including dental pain (Wyant, 1979; Curtis, 1980; Levine, 1999).

Somatic modulation of tinnitus

Even before entering our clinic, ~20% of patients have already noticed that they can “somatically modulate” their tinnitus, for instance alter the loudness or pitch of their tinnitus by clenching their teeth together or pushing on various places on the head (Levine and Kiang, 1995). The following presentation of tinnitus is a case in point.

Case 2. (Part 1) A 42-year-old man with normal pure tone thresholds reported that about a year earlier he had developed a constant “choppy tone” in his left ear that he could stop momentarily by biting down hard, or poking at his ear in various ways [see p.204 (PART 2)].

Cases like this one prompted us to systematically examine our patients with a battery of isometric head, neck and jaw contractions (“somatic testing” Table 1). We found that ~80% of tinnitus patients can transiently modulate their tinnitus to variable degrees with one or more of these maneuvers (Levine et al., 2003). A variety of changes can occur. Most commonly the tinnitus gets louder, but many times the tinnitus can become quieter. Less frequently patients describe pitch or location changes.

To assess whether somatic modulation is a general phenomenon and not restricted to individuals

Table 1. Somatic testing: maneuvers currently being used to test for tinnitus modulation

Jaw contractions	
1.	Clench teeth together
2, 3.	Open mouth, with and without restorative pressure
4, 5.	Protrude jaw, with and without restorative pressure
6, 7.	Slide jaw to left, with and without restorative pressure
8, 9.	Slide jaw to right, with and without restorative pressure
10.	Retract jaw
Head and neck contractions	
With the head in the neutral position, contractions were made to resist pressure applied by the examiner to:	
11.	forehead
12.	occiput
13.	vertex
14.	left temple
15.	Right temple
16.	with the head turned to the left, resist the tortional force on the left zygoma
17.	with the head turned to the right, resist the tortional force on the right zygoma
18.	with the head turned to the right and tilted to the left, resist force applied to the left temple (left sternocleidomastoid)
19.	With the head turned to the left and tilted to the right, resist force applied to the right temple (right sternocleidomastoid)
Pressure on muscle insertions	
20.	right mastoid attachment of sternocleidomastoid
21.	left mastoid attachment of sternocleidomastoid
22.	right suboccipital attachment of splenius capitis
23.	left suboccipital attachment of splenius capitis
	Posterior pinna pressure
24.	right pinna attachment of posterior auricular
25.	Left pinna attachment of posterior auricular

Note: all maneuvers use maximal force applied by the examiner.

who seek help for their tinnitus, we tested somatic modulation in 62 adult volunteers (Abel and Levine, 2004). Our only exclusion criterion was that they had never sought medical care for tinnitus. Twelve subjects (19%) knew that they had tinnitus, but did not consider it a problem; another 17 (27%) were unaware that they had tinnitus until they were brought into a room with very low-level ambient noise and were asked what they heard; the remaining 33 participants had no tinnitus even in quiet and even when pointedly questioned. Among the 29 people with tinnitus, 23 (again ~80%) could modulate their tinnitus with somatic testing. Hence, somatic modulation of tinnitus is not restricted to the clinical population; its incidence (80% with our test battery) appears to be the same for all populations with tinnitus and perhaps all causes of tinnitus. This fact implies that the ability

to modulate tinnitus somatically is not what makes tinnitus a clinical problem.

In the 33 people with no tinnitus whatsoever, somatic testing elicited an acoustic percept (“tinnitus”) in 19, or almost 60%. This observation suggests that somatic modulation of auditory function occurs commonly but only happens to be most obvious in people with tinnitus because they have an ongoing auditory percept (Sanchez et al., 2002; Abel and Levine, 2004).

An obvious question is whether the changes in tinnitus induced by somatic maneuvers might be caused by maneuver-induced sounds or changes in the auditory periphery (e.g., middle ear muscle contractions which might modulate externally or internally generated sounds). To examine this possibility, we somatically tested people who are deaf (individuals with cochlear implants with their

implant disconnected) (Levine et al., 2003). Fourteen deaf individuals, 11 with ongoing tinnitus and 3 without tinnitus were tested in our standard manner (“somatic testing”). Six of the 11 (54%) with ongoing tinnitus could modulate their tinnitus with somatic stimulation, and 2 of the 3 (67%) without tinnitus could elicit an auditory percept with somatic testing. These percentages are close to those for people with hearing (54% and 60% as compared to 80% and 60% — “close” given the relatively small sample of deaf subjects). The nature of the tinnitus changes in deaf people was also comparable to those in hearing individuals. The prevalence of somatically induced tinnitus and tinnitus changes in deaf people strongly suggests that the strikingly similar effects in hearing people are not mediated acoustically, but instead arise from neural interactions between the somatosensory and auditory systems. The fact that somatic maneuvers most commonly changed tinnitus loudness in both hearing and deaf people suggests that the changes in both groups were subserved by the same neural mechanisms.

Given this evidence, the following conclusion seems almost inescapable: that somatosensory–auditory neural interactions within the central nervous system account for most, if not all, somatic modulations of tinnitus, as well as, the development of auditory percepts with somatic testing in those with no tinnitus.

There is good evidence that somatic modulation of tinnitus may be a special case of the general principle that auditory function can be modified by somatosensory input. One line of evidence comes from animal studies showing substantial convergence of the somatosensory system on nominally “auditory” centers throughout the brain (Aitkin, 1986; Shore et al., 2000). Another comes from direct demonstrations of somatosensory–auditory interactions in people (Lewald and Ehrenstein, 1998; Lewald et al., 1999). One study, particularly relevant in the present context, used electrical stimulation of the median nerve at the wrist as the somatic stimulus to induce alterations in the perception of external sound (Møller and Rollins, 2002). Sixty percent of participants (especially children) reported changes in the perception of external sounds to the stimulus. Of those whose perceptions

were altered, all perceived a change in the loudness of the external sound (83% louder, 17% quieter). In an earlier study examining the effects of the same somatic stimulus (electrical stimulation of the median nerve) in people with tinnitus, Møller et al. (1992) found that tinnitus was modulated in close to 40% of participants. This percentage is much lower than that showing tinnitus modulation with somatic maneuvers, most likely because an upper extremity was stimulated, rather than the most sensitive regions for inducing somatic modulation, the lateral upper neck and head.

If the apparent difference in efficacy of median nerve stimulation vs. somatic maneuvers for changing tinnitus generalizes to external sounds, the already substantial percentage of people experiencing a somatic influence on the perception of external sounds found by Møller and Rollins, may underestimate the prevalence of somatic influences on the perception of external sound. In other words, even more individuals would have modulated their perception of an external sound with somatosensory stimulation at other locations such as the lateral upper neck and head (see Chapter 1). Indeed, if the strength and number of projections from somatosensory to auditory system are any indication, somatic influences on everyday sound perception may be considerable (Lewald and Ehrenstein, 1998; Lewald et al., 1999).

Somatic tinnitus syndrome

Our finding that people without tinnitus (even when specifically questioned in a very low-ambient noise environment) can develop tinnitus from forceful head and neck contractions suggests that some cases of clinical tinnitus may be due to abnormal activation of somatic–auditory interactions. Case 2 (begun above) is one such example.

Case 2. (Part 2) Approximately 6–8 weeks following the onset of chronic upper left dental discomfort from treatment of left upper molar decay, a 42-year-old man with normal pure tone thresholds developed left-sided tinnitus. Because of the discomfort he would avoid biting on the left. Ultimately his tooth repair was revised and his

dental discomfort resolved after which his left-sided tinnitus gradually became fainter. When evaluated in our clinic about a year following his dental revision, his tinnitus was not heard. However on examination increased muscle tension involving his left sternocleidomastoid muscle was detected independently by two different examiners, neither of whom had any knowledge of his tinnitus. With somatic testing left sternocleidomastoid contraction elicited a faint sound in his left ear only, whereas right sternocleidomastoid contraction elicited no sound perception (see Chapter 19).

Consider another such example.

Case 3. An 80-year-old woman was hearing impaired (75 dB flat loss was present at all frequencies above 500 Hz) for more than 40 years but denied ever having prior tinnitus. She reported stumbling and striking her left forehead against a doorframe after which she developed an intermittent, mild left-sided headache. Three days after the trauma, she developed very distressing intermittent left ear tinnitus [“like a loud blender”], but she noted no other change in her hearing. Her pure tone hearing loss was unchanged as compared to an audiogram from 8 months earlier. Her hearing thresholds were similar for both ears except at 500 Hz, where the left ear threshold was 25 dB better than the right. Speech discrimination scores were ~85% bilaterally. She had been using hearing aids for more than 30 years, and had a strong family history of hearing loss. On examination her left sternocleidomastoid was non-tender but was under increased tension as compared to the right. The suboccipital insertion of her left splenius capitis was, however, focally tender. Somatic testing did not modulate her tinnitus. But with a cervical exercise program her tinnitus resolved within 3 months of its onset.

These two case reports illustrate the three characteristics of the “somatic tinnitus syndrome.” First, the tinnitus begins shortly (if not immediately) after a disturbance of the lateral head or upper neck. We have never encountered patients in whom disturbances of the upper extremities, torso,

or lower extremities led to tinnitus, nor have others reported such findings. Thus, there appears to be a predilection for the periauricular region and particularly the upper lateral neck muscles in tinnitus (see Chapter 1). Second, the tinnitus is always perceived as ipsilateral to the somatic event and usually in the ear. Third, the onset of tinnitus is not associated with any other, new hearing complaints, new vestibular symptoms or abnormalities on neurological examination. The syndrome can occur in people with or without hearing loss. Pure tone hearing thresholds and speech discrimination scores of the two ears are usually similar and often within normal limits. Hyperacusis is not a common feature of such individuals. In general successful treatment of the somatic disorder associated with the tinnitus can also resolve the tinnitus itself (Cases 2 and 3).

Because somatic tinnitus is commonly a part of the TMD syndrome (59% [Chole and Parker, 1992](#)), it follows that the other components of TMD, namely, ipsilateral facial pain, ear pain or pressure, occipital or temporal headaches, and facial paresthesias can be associated with the somatic tinnitus syndrome as well ([Chole and Parker, 1992](#)).

The fact that both auditory factors and somatic factors can play a role in the genesis of tinnitus implies that in some people it may be an interaction between these two factors that leads to their tinnitus (see Chapter 10). In Case 3 (above), the pre-existing hearing loss, and any resulting modifications of the central auditory system, may have set the stage for the development of tinnitus following somatic injury. Similarly, a somatic disturbance of the head and upper neck can be a predisposing factor for the development of sound-induced tinnitus as illustrated by the following.

Case 4. A 43-year-old man had had a history of bruxism and chronic left dental and sinus pain for more than a year. As a result of bruxism he had cracked his left upper canine tooth and ultimately received a dental implant. His hearing thresholds were normal. Approximately 6 months after his implant he attended a loud 3-h concert. By 1 h of the concert he developed sharp ear pains worse on the left and diminished hearing bilaterally. Both

ears were felt to be equally exposed to the high-level sounds. After the concert he experienced bilateral ear pressure that resolved over an hour. Two hours following the concert he experienced left ear “ocean wave” tinnitus that became louder with jaw opening and protrusion. His tinnitus resolved after 36 h. Later an audiogram showed no change in hearing thresholds and jaw opening and protrusion could not induce any tinnitus.

Note that despite symmetric hearing and symmetric high-level sound exposure with symptoms of bilateral temporary threshold shift his tinnitus developed only on the side with chronic facial pain.

Dorsal cochlear nucleus inhibition hypothesis

A neurological model can account for the major features of otic [ear-related] and somatic tinnitus

(Fig. 1). Recall that somatic modulation of tinnitus can occur in deaf individuals. This implies that somatic modulation occurs because of interactions between the somatosensory and auditory systems within the central nervous system. Because the tinnitus of the somatic tinnitus syndrome is usually perceived in one ear, this suggests that the somatosensory–auditory interactions occur within the afferent central auditory pathway prior to the auditory decussation, i.e., before the level of the superior olivary complex, trapezoid body. The only auditory nuclei before the auditory decussation are the dorsal cochlear nucleus and ventral cochlear nucleus.

Findings of neural hyperactivity in dorsal cochlear nucleus following acoustic trauma and cisplatin ototoxicity in animals have led to the hypothesis that the dorsal cochlear nucleus is the likely site of origin of the neural hyperactivity associated with tinnitus (Kaltenbach et al., 2005)

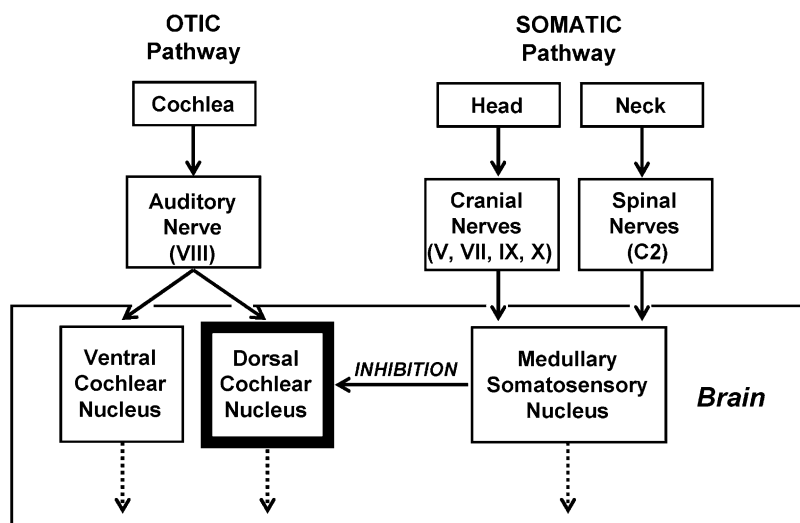


Fig. 1. Schematic depiction of the anatomic basis for the dorsal cochlear nucleus hypothesis: both somatic and otic (ear) tinnitus occurs owing to disinhibition of the dorsal cochlear nucleus. In both cases, tinnitus is due to increased activity in the output of the dorsal cochlear nucleus, which projects to the other centers and eventually leads to activation of the auditory perceptual machinery responsible for tinnitus. For somatic tinnitus sensory inputs from (1) the face via the trigeminal (V) nerve in the spinal trigeminal tract; (2) the external and middle ears via the common spinal tract of the facial (VII), glossopharyngeal (IX), and vagus (X) cranial nerves; and (3) the neck via the C2 dorsal spinal root converge to a common region of the lower part of the medulla, the medullary somatosensory nucleus, from which fibers project to the ipsilateral dorsal cochlear nucleus. Modulation of activity in the medullary somatosensory nucleus to dorsal cochlear nucleus pathway results in disinhibition of the dorsal cochlear nucleus. For otic tinnitus, loss of input (spontaneous activity) from the auditory (VIII) nerve leads to disinhibition of the dorsal cochlear nucleus.

(see Chapter 9). Somatic modulation likewise can be accounted for by invoking somatosensory influences on the dorsal cochlear nucleus. From the first observation of an anatomical connection between the somatosensory system and dorsal cochlear nucleus more and more evidence has been accumulating regarding this connection (Itoh et al., 1987; Weinberg and Rustioni, 1987). These results culminated with the Kanold and Young cat study (Fig. 2), where they showed that of all the nerves tested extending from the face to the hindlimbs, the C2 dorsal nerve root had the largest impact on the responses recorded from the cells in the ipsilateral dorsal cochlear nucleus (Kanold and Young, 2001). Furthermore it was somatosensory stimulation, muscle stretch or vibration, which was the most potent modulator of dorsal cochlear nucleus activity, as opposed to cutaneous stimulation such as light touch, brushing of hairs, or stretching of skin.

These findings obtained in the cat are perfectly concordant with our clinical findings regarding somatic modulation, namely, that (a) muscle activation is the most potent modulator of tinnitus, as opposed to cutaneous stimulation such as light touch, brushing of hairs, or stretching of skin and (b) the muscles of the upper cervical region [C2]

are the most potent somatic modulators of tinnitus. Finally the projections from the somatosensory nuclei (nucleus cuneatus/medullary somatosensory nucleus) to the dorsal cochlear nucleus are only ipsilateral just as the somatic tinnitus syndrome is always ipsilateral to the cervical or dental insult. We have formalized these hypotheses by proposing that the dorsal cochlear nucleus disinhibition hypothesis can account for some forms of tinnitus on an auditory or somatosensory basis, as well interactions between the two (Fig. 1) (Levine and Kiang, 1995; Levine, 1999).

Why somatosensory projections to the dorsal cochlear nucleus?

A functional role for the somatosensory projections from the upper cervical region to the dorsal cochlear nucleus can be suggested from evidence that the dorsal cochlear nucleus is involved in up-down and front-back sound localization in animals (Sutherland et al., 1998). The convergence of the (i) acoustic and (ii) upper cervical proprioceptive information allows the dorsal cochlear nucleus to integrate (a) sound localization information extracted from the acoustic inputs reaching

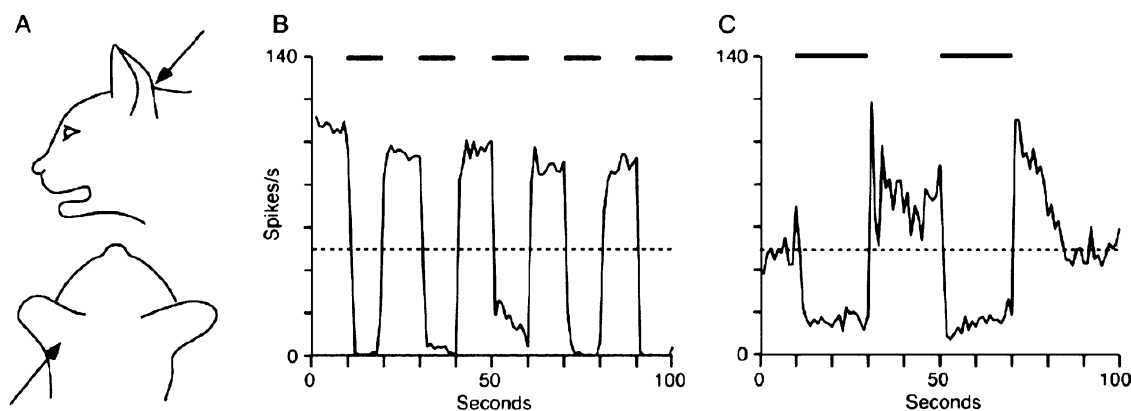


Fig. 2. Responses of dorsal cochlear nucleus (type IV) neurons to stretch of cat pinna muscles. Panels B and C show the responses of two different neurons to manual pressure (indicated by the bars above the plots) applied to the pinna as shown in A. The effect of the pinna pressure was continuous inhibition, maintained as long as the pressure was applied. The effect of pinna pressure is mediated through the following neural pathway: C2 spinal nerve to fasciculus cuneatus to medullary somatosensory nucleus to ipsilateral dorsal cochlear nucleus (Fig. 1). Muscle stretch or vibration was the most potent modulator of dorsal cochlear nucleus activity. Cutaneous stimulation (light touch, brushing of hairs, or stretching of skin) had no effect. Adapted with permission from Kanold and Young (2001).

the ear with, (b) head position information extracted from the somatosensory inputs. From integrating these two kinds of information the central nervous system can infer where in space a sound source is located.

Recently, it has been suggested that the trigeminal somatosensory inputs from the jaw muscles to the dorsal cochlear nucleus projections are present to suppress self-generated sounds such as respiration, chewing, or self-vocalizations (Shore and Zhou, 2006).

We conclude that somatosensory–auditory neural interactions within the dorsal cochlear nucleus can account for (a) somatic modulation of tinnitus, (b) inducing tinnitus in non-tinnitus individuals by strong muscle contractions of the head and neck testing, and (3) the somatic tinnitus syndrome.

Tinnitus treatments utilizing somatosensory–auditory interactions

Given that the somatosensory, as well as the auditory system, plays a role in the generation of tinnitus, the important question from a clinical standpoint is whether treatments targeting the somatosensory system can be utilized to treat tinnitus with predictable success. Such treatments include acupuncture (Hansen et al., 1982; Axelsson et al., 1994), electrical stimulation of the scalp and auricle (Engelberg and Bauer, 1985; Dobie et al., 1986; Lyttkens et al., 1986), cervical manipulation (Alcantara et al., 2002; Hulse and Holzl, 2004; Whedon, 2006), craniosacral therapy, TMD treatments (Wright and Bifano, 1997b), and trigger point treatments (Eriksson et al., 1995) including injections (Wyant, 1979; Estola-Partanen, 2000) (see Chapters 18 and 19).

Previous reports indicate that a range of such treatments can be effective, at least in isolated cases. It is likely that many of these successful treatments are mediated through central somatosensory–auditory interactions. If so, there may be a subgroup of patients whose tinnitus improves with appropriate activation of the somatosensory system.

We undertook a systematic evaluation of the literature to determine whether or not people likely to have tinnitus of somatic origin responded to treatment modalities involving the somatosensory system.

Since the examples reported in the literature rarely include all the information needed to assign a definitive somatic genesis of tinnitus, we had to rely on incomplete information. Recall that the somatic tinnitus syndrome includes (a) tinnitus that is always perceived as ipsilateral to the somatic event and usually in the ear and (b) the onset of tinnitus is not associated with any new hearing complaints. Hence tinnitus that is (a) strongly lateralized to one ear and (b) associated with symmetric hearing would be most suspects for having a strong somatic component to its etiology. Likewise people with tinnitus strongly lateralized to one ear despite symmetric hearing thresholds may be most responsive to treatment modalities mediated through the somatosensory system.

Characteristics of responders to somatosensory treatments

Cervical manipulation

Successful alleviation of tinnitus by cervical manipulation has been reported. However, the reports are strictly anecdotal and provide little detail and no information about the hearing in the patients discussed (Alcantara et al., 2002; Whedon, 2006). Thus, the characteristics of the patients responding to this treatment modality are largely unknown.

Acupuncture

Studies of acupuncture for tinnitus show a definite pattern regarding who derives benefit: people with tinnitus strongly lateralized to one side and symmetric hearing thresholds. The symmetry of hearing combined with the asymmetry of the tinnitus, makes a solely auditory origin to the tinnitus unlikely. Our suspicion is that many of the responders to acupuncture are people with somatically induced tinnitus.

The most striking published case in the acupuncture literature is that of a 60-year-old man whose tinnitus was predominantly referred to the left ear. His hearing thresholds differed by less than 10 dB between ears. He “experienced a marked improvement after the first [periauricular and extremities] acupuncture session and the reduction in tinnitus lasted several months (Axelsson et al., 1994).” In another similar case a 45-year-old woman with chronic tinnitus referred to the right ear and no hearing loss had complete resolution of her tinnitus with one session of right periauricular acupuncture (Jing Liu, LicAc, personal communication). Yet another example comes from our clinic. The following patient was seen subsequent to a dramatic response to periauricular acupuncture.

Case 5. A 77-year-old man had had 20 years of left ear tinnitus. He had symmetric, sensorineural hearing loss (SNHL) ranging from 20 dB at 250 Hz to 70 dB at 4 and 8 kHz with approximately 70% speech discrimination. For the first 15 years his tinnitus would recur intermittently at a low level with periods of no tinnitus for up to 2 weeks. Over the next 5 years his tinnitus was intermittently louder, especially after dozing in a chair. Six months prior to his visit to our clinic his tinnitus became constant, loud, and “throughout my head” leading to depression, including a suicide attempt. His hearing thresholds were unchanged.

Two months prior to his visit he started twice-weekly acupuncture (periauricular, suboccipital, and extremities). With his third treatment his tinnitus suddenly changed from bilateral to left unilateral and the tinnitus was no longer bothersome. Following that event he completed 3 weeks of acupuncture (as recommended). His tinnitus then remained in the left ear at a very low level except for a 5-day period when it was transiently louder. At his clinic visit, with somatic testing his left ear tinnitus modulated only slightly; its loudness went from 1 to 2 on a 0–10 scale with left jaw deviation or pressure on the sternocleidomastoid tendon at the left mastoid. Multiple maneuvers including right sternocleidomastoid contraction caused the

Table 2. Data from Hansen et al. (1982)

Hearing	Subjects (M/F)	Improved	Not improved
Normal	2 (0/2)	2	0
Impaired bilateral	7 (4/3)	2	5
Impaired unilateral	8 (5/3)	0	8
Total	17 (9/8)	4	13

Note: Tinnitus: all unilateral; 4 intermittent.

development of transient right ear tinnitus that increased in loudness from 0 to 4 on a scale from 0 to 10. Over the next 12 months his tinnitus remained constant despite another 3-week course of acupuncture. However 1 year after his clinic visit his constant left tinnitus stopped abruptly and spontaneously. It then became intermittent, as it had been for his first 15 years.

Besides these isolated, but nevertheless striking cases, one acupuncture report described the systematic treatment of tinnitus patients all of whom had chronic unilateral tinnitus (Hansen et al., 1982). The patients were mixed in whether or not they had hearing loss. Table 2 organizes their data according to the individuals’ pattern of hearing loss. Note that all periauricular acupuncture points were considered equivalent whether or not they were placed in the classical Chinese points or nearby “placebo” points. Tinnitus was intermittent in 24% of the participants, but the paper does not indicate which had intermittent tinnitus.

Two results in Table 2 are particularly noteworthy: (1) the two patients with normal hearing and unilateral tinnitus both improved. The hearing thresholds and tinnitus of these people suggests a predominantly somatic origin for their tinnitus. (2) None of the patients with unilateral hearing loss and unilateral tinnitus responded. The concordance between tinnitus and hearing loss makes an auditory, rather than somatic genesis of the tinnitus more likely in these people. Thus, the results for two categories of patients indicate that having two hallmark signs of somatic tinnitus (lateralized tinnitus, symmetric hearing thresholds) predicted a positive response to acupuncture.

The seven remaining individuals had bilateral hearing loss, but Hansen et al. do not describe

Table 3. Data from [Lyttkens et al. \(1986\)](#) (all with slight to moderate bilateral sensorineural hearing loss)

Subj #.	Age	Sex	Tinnitus					Match	
			Side	Yrs	Fluct?	RI	Mask	kHz	dB
1	75	M	L	20	N	N	90	0.4	45
2	68	F	L	12	Y	N	80	0.16	75
3	42	M	L	2	N	Sl	60	6.3	70
4	44	M	Both	1	N	N	70	7.0	60
5	52	M	Both	2	N	N	50	3.1	60

Fluct = fluctuating
RI = residual inhibition
N = no
Y = yes
Sl = slight
Mask = masking level.

whether or not the loss was symmetric. Therefore, we do not know whether the results for this group follow those of the other two hearing groups just described (normal and unilateral loss). If they did, the two responders with bilateral hearing loss would have had symmetric hearing (and likely tinnitus triggered somatically) and the five non-responders would have had asymmetric hearing (and likely tinnitus of predominantly auditory origin). In other words, the responders would be those judged most likely to have somatically triggered tinnitus.

Electrical stimulation of the scalp and auricle

More complete case descriptions are reported in two reports on electrical stimulation. In one study electrical stimulation of the skin over the mastoid with a “Theraband” was used in five individuals with tinnitus and symmetric hearing loss (slight to moderate) ([Lyttkens et al., 1986](#)). Only participant no. 2 had any true tinnitus suppression ([Table 3](#)); for the first time in 12 years she did not hear her tinnitus. She was the only participant whose tinnitus fluctuated in addition to being unilateral. This fluctuating, unilateral tinnitus, combined with symmetric hearing strongly suggests somatically-induced tinnitus. A second report ([Engelberg and Bauer, 1985](#)) describes the effect of electrical stimulation of the earlobe in nine individuals with chronic tinnitus ([Table 4](#)). Only participant no. 7

Table 4. Data from [Engelberg et al. \(1985\)](#)

Subj #	Age	Sex	Tinnitus			Match
			Side	Yrs	Hearing	
1	47	F	Both	15	SNHL	5.8/2.8
2	68	M	Both	38	SNHL	5.3/4.3
3	69	M	Both	8	SNHL	2.6/2.7
4	40	M	Both	20	SNHL	3.6/3.8
5	36	M	Both	3	SNHL	2.6/2.2
6	40	M	Both	20	SNHL	5.5/5.2
7	23	F	Right	1	Normal	7.0
8	34	M	Both	12	SNHL	3.1/4.0
9	32	F	Both	27	SNHL	5.0/?

SNHL = sensorineural hearing loss.

experienced full suppression of her tinnitus. She was the only individual with unilateral tinnitus and symmetric (normal) hearing; all others had bilateral tinnitus.

A third electrical stimulation report provides less detail but used the same device, the “Theraband,” and placement as [Lyttkens et al. \(Dobie et al., 1986\)](#). As in the [Lyttkens et al.](#) study, one of the 20 participants had a definite response. This person responded with an 85% reduction in his tinnitus loudness. His tinnitus was described as asymmetric (“left>right”) and his hearing loss was “mildly asymmetric”. There is no description of the direction of the asymmetry so it is unknown whether it was the same or different from the tinnitus. Both this and [Lyttkens et al.’s](#) “Theraband” study were effectively placebo-controlled, since nothing was heard or felt when the device was activated.

Trigger point treatments

Trigger point injections of the cervical and jaw muscles can transiently abolish tinnitus (see Chapter 18). It has been reported in a large statistical study of 178 “non-selected primary care ENT patients,” ([Estola-Partanen, 2000](#)) as well as in anecdotes ([Wyant, 1979](#)). The statistical study found that within 5–10 days of injection the tinnitus disappeared in ~15% of these patients. By 6 months after the last in a series of trigger point injections, more than 30% of the patients felt

improved, as compared to ~15% of a control group (Estola-Partanen, 2000). The study also found that the most cervical tension occurred on the side to which the tinnitus was referred. Women responded better than men and “chirping” tinnitus better than other descriptions.

The anecdotes include a woman with recent onset of tinnitus referred to her right ear in which she had no hearing since a labyrinthectomy 12 years earlier (Wyant, 1979). The tinnitus she referred to her right ear was associated with occipital headache radiating to the vertex and the eyes. With a steroid and lidocaine injection of her right splenius and scalenus medius trigger points her headache and tinnitus resolved promptly. The injections were repeated eight times; the relief lasted from several days to 4 weeks.

A second patient had mid-cervical pain radiating to the left face and eye, accompanied by tinnitus referred to the left ear. Injection of multiple left cervical trigger points with steroid and lidocaine provided relief of both tinnitus and pain for 4 months. No mention was made of his hearing status (Wyant, 1979).

Massage and stretching of trigger points have also eliminated tinnitus in some patients for up to 24 h (Eriksson et al., 1995).

TMD treatments

Several reports have described the effects of non-operative TMD treatment on tinnitus in TMD patients (Bernstein et al., 1969; Gelb and Tarte, 1975; Bush, 1987; Rubinstein and Carlsson, 1987; Kerstein, 1995; Wright and Bifano, 1997a). The reports are not explicit but most of the participants in these studies appear to have had normal hearing and tinnitus ipsilateral to their TMD (Curtis, 1980). Tinnitus resolved in over 50% of those who rated “their tinnitus as moderate or severe (Wright and Bifano, 1997a),” and in up to 65% of less severe cases (Wright and Bifano, 1997b). Pure tone hearing threshold data is not presented. But of those who responded to TMD treatments 70%

(23 of 33) felt that their hearing ipsilateral to their tinnitus was normal, whereas all of those who did not respond to treatment felt their hearing ipsilateral to their tinnitus was not normal (Wright and Bifano, 1997a). Note the similarity to the Hansen et al. (1982) data (Table 2).

Furthermore, Wright and Bifano did some limited somatic modulation testing on the participants in their study and found a significant association between the ability to modulate tinnitus with “maximum voluntary clenching” and improvement or resolution of tinnitus with their TMD treatment program. Thus this study is consistent with the thesis that somatic testing can predict which subgroup of patients with TMD will benefit from TMD treatment for their tinnitus.

The finding of an association between response to somatic testing and the outcome of tinnitus treatment is unique among tinnitus treatment studies. No studies using auditory assessments of tinnitus such as residual inhibition, minimal masking level, tinnitus loudness, and level matching, otoacoustic emissions, evoked potentials, etc. have found any correlation between the test results and the outcome of treatment.

Conclusions

This review of the literature and our clinical experience of treatment of tinnitus patients with different modalities involving the somatosensory system show that the tinnitus of some patients improves with such treatments. Only one report made any attempt to restrict their study group by the characteristics of their tinnitus. While the Hansen et al. (1982) investigation was designed to detect a difference in tinnitus benefit depending on acupuncture location, in effect, by choosing the unilateral tinnitus subgroup, their results do identify a subgroup of individuals with tinnitus who respond to acupuncture, namely, those with unilateral tinnitus that is not caused by an ear disorder. This finding is supported by other studies employing treatments likely involving the somatosensory system (Wyant, 1979; Engelberg and Bauer, 1985; Dobie et al., 1986; Lyttkens et al.,

1986; Axelsson et al., 1994; Wright and Bifano, 1997a; Estola-Partanen, 2000).

Furthermore, there is support for the notion that the subgroup of individuals with unilateral tinnitus that responds best to somatosensory treatments is those whose tinnitus is fluctuating. Two extreme kinds of fluctuating tinnitus are (a) intermittent tinnitus and (b) tinnitus that can be unilateral when quieter and non-lateralized when louder.

It is our conclusion that treatments for tinnitus that involve the somatosensory system should be restudied employing a design that tests the following hypothesis: individuals with unilateral fluctuating tinnitus and symmetric pure tone hearing significantly benefit from these treatments.

Abbreviations

SNHL	sensorineural hearing loss
TMD	temporomandibular disorder

Acknowledgments

Jing Liu, LicAc for sharing his experience treating tinnitus patients with acupuncture. We gratefully acknowledge the support of the Tinnitus Research Initiative, Jack and Shelley Blais, Kenneth and Anne Griffin, Kangwon National University Overseas Faculty Research Program 2005 (EC Nam), and the American Tinnitus Association.

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CHAPTER 18

Myofascial trigger points: another way of modulating tinnitus

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Abstract: Tinnitus is a multifaceted symptom that may have many causes (otologic, neurological, metabolic, pharmacological, vascular, musculoskeletal and psychological) several of which often occur in the same patient. Tinnitus can often be modulated by different kinds of stimuli. In this chapter we describe the results of a study of modulation of tinnitus from stimulation of myofascial trigger points (MTPs). MTPs are small hypersensitive areas in palpable taut bands of skeletal muscles found in patients with the myofascial pain syndrome where stimulation of MTPs causes local and referred pain. We found a strong correlation between tinnitus and the presence of MTPs in head, neck and shoulder girdle ($p < 0.001$). In 56% of patients with tinnitus and MTPs, the tinnitus could be modulated by applying digital compression of such points, mainly those of the masseter muscle. The worst tinnitus was referred to the side that had the most MTPs ($p < 0.001$); Compression of the trigger point on the same side as the tinnitus was significantly more effective than the opposite side in six out of nine of the studied muscles. Compression of MTPs was most effective in patients who have had chronic pain earlier in the examined areas.

Keywords: tinnitus; myofascial trigger points; muscle; chronic pain; myofascial pain syndrome; referred pain

Introduction

The causes of tinnitus may involve neurological, metabolic, pharmacological, vascular, musculoskeletal and even psychological factors (Møller, 1984; Møller, 2003; Sanchez and Bento, 2000; McCombe et al., 2001; Sanchez et al., 2005) and it is not uncommon to find more than one possible cause in the same patient (Marion and Cevette, 1991; Sanchez et al., 2005).

Many forms of tinnitus can be modulated by muscle contractions or maneuvers of head, neck

and limbs (Levine, 1999; Sanchez et al., 2002), electrical stimulation of the median nerve (Møller et al., 1992), alteration of gaze (Cacace, 2003) and pressure applied to the temporomandibular joint (Rubinstein et al., 1990). Travell and Simons (1983) were the first to report that perception of sound could be evoked, by a trigger point palpated in the superficial parts of the sternal division of the sternocleidomastoid. The sound was referred to the ipsilateral ear. The person had no spontaneous tinnitus. Later, Eriksson et al. (1995) described a patient who noticed differences in tinnitus when palpating a trigger point in the same muscle division described by Travell and Simons. In a recent study we examined the involvement of myofascial

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trigger points (MTPs) in tinnitus and found a strong link between tinnitus and MTPs (Rocha et al., 2006).

MTPs are small hypersensitive areas located in palpable taut bands of skeletal muscles that, either spontaneously or under mechanic stimulation, can cause local and referred pain with a well-defined pattern for each muscle (Travell and Simons, 1999; Møller, 2006). Snapping palpation (compression across the muscle fibers rapidly) of the MTPs may elicit a brisk contraction of the muscle fibers in or around the taut band (Travell and Simons, 1999).

MTPs are considered active (AMTPs) when stimulation causes referred pain that is similar to a patient's usual pain recognition or when it aggravates existing pain (Aronoff, 1998). They are frequently found on postural muscles of the neck, shoulder and pelvic girdle as well as in masticatory muscles, where they provoke spontaneous pain or movement-related pain (Davidoff, 1998). Latent MTPs (LMTPs), in turn, are located in symptom-free areas and only provoke local and referred pain when stimulated (Hong and Hsueh, 1996). LMTPs are less sensitive to palpation and much more frequent in the general population than MTPs (Travell and Simons, 1999). Fifty percent of normal asymptomatic persons have LMTPs on examination of the shoulder girdle musculature (Sola et al., 1955).

Individuals with MTPs may also complain of tinnitus. We found that out of the 68 individuals with tinnitus and MTPs, 55.9% reported temporary tinnitus modulation upon digital pressure of at least one point (Rocha et al., 2006) and that deactivation of such points to treat myofascial pain, also reduced the tinnitus or even made it disappear in some individuals, indicating a relationship between some forms of tinnitus and MTPs. There is considerable evidence of similarities between tinnitus and other forms of pain (Møller, 1997, 2006) (see also Chapter 4).

Prevalence of MTPs in tinnitus patients

LMTPs and AMTPs are commonly present in patients with tinnitus (Rocha et al., 2006). In this study of 94 tinnitus patients, 72.3% had MTPs in

at least one of the examined muscles compared with 36.2% in the control group of individuals without tinnitus. Eriksson et al. (1995) also reported a significant difference between the rate of MTPs in individuals with and without tinnitus. Many factors related to tinnitus such as depression, anxiety, temporomandibular joint dysfunction, hypoglycemia, hypothyroidism, sleep disturbances, may predispose for MTPs.

Myofascial pain is a complex disorder that is poorly understood. Much research has been devoted to studies of the basis of for these trigger points. Some studies have indicated that they may represent spinal reflexes.

Lateralization of tinnitus and MTPs

Activation of MTPs on one side of the body influences tinnitus on the same side in 56.5% ($p < 0.001$) of the participants in the study of 94 individuals with tinnitus mentioned above, or on the side of the worst tinnitus (Rocha et al., 2006). Estola-Partanen (2000) found a statistically significant lateralization of ($p < 0.001$) tinnitus to the side of the body with muscular tension and pain related to MTPs in neck muscles and shoulder girdle. Bjorne (1993) (see Chapter 19) reported that 39 individuals with tinnitus had hypersensitive spots in the lateral pterygoid muscle. In the individuals who had unilateral tinnitus (29 of the 39 participants) the tinnitus was referred to the same side as the MTPs. Travell (1960) and Wyant (1979) have also reported that tinnitus that was associated with MTPs was referred to the same side as where pain could be elicited by stimulation of MTPs.

That tinnitus and pain were referred to the same side may be explained by the existence of connections between proprioceptive and nociceptive afferents from the neck region to the cochlear nucleus (Itoh et al., 1987; Young et al., 1995; Wright and Ryugo, 1996) (Chapters 9 and 10). Levine (1999), in turn, suggests that somatic stimuli can disinhibit the ipsilateral cochlear nucleus, producing excitatory neuronal activity within the auditory pathway that results in tinnitus. The fact that tinnitus lateralizes to the side of the somatic

injury support the hypothesis of a somatosensory component in the origin of some forms of tinnitus. Increase in tinnitus can also be explained by the effect of projections of the cuneate nucleus to the cochlear nucleus (Wright and Ryugo, 1996). The dorsal column nuclei in the somatosensory system are similar to that of the cochlear nucleus in the auditory system being the first relay nuclei of sensory information. Afferent fibers from the neck, ear and suboccipital muscles terminate in the lateral part of the cuneate nucleus. There are connections from cells in the cuneate nucleus and the dorsal cochlear nucleus (Young et al., 1995; Wright and Ryugo, 1996) making up the anatomical basis for modulation auditory information.

Modulation of tinnitus by MTPs

In a recent study of 68 patients with both tinnitus and MTPs (Rocha et al., 2006) we found that digital compression of MTPs located in head, neck and shoulder girdle muscles could modulate the tinnitus in 55.9% of the participants in the study; and both the intensity and the type of sound were affected. In more than 65% of these participants the tinnitus was aggravated by the stimulation of the MTPs whereas others experienced a decrease in the loudness or that the tinnitus disappeared altogether. The MTPs from which tinnitus could be manipulated were most often located in the masseter, splenius capitis, sternocleidomastoid or temporalis muscles.

MTPs located in head and neck muscles produced more tinnitus modulation than those located in the shoulder girdle, which supports the finding of Levine (1999) and Sanchez et al. (2002) who showed that head and neck muscular contraction maneuvers produced more modulation than those of other muscles.

There is evidence that aberrant neuronal activity in auditory pathways of tinnitus patients may be increased through excitatory stimulation of the dorsal column nuclei though their connection to the dorsal cochlear nucleus, and that may explain why tinnitus may increase by activation of the somatosensory system such as through stimulation of MTPs. According to Wang and Audette (2000),

there are significant segmental differences in the central nervous system at the level of the spinal cord between individuals with AMTPs and LMTs but not peripherally in the muscle itself. AMTPs are closely related to spinal cord integration and central facilitation and supports the theory that myofascial pain has a neuromuscular cause. We initially believed that only AMTPs would be able to modulate tinnitus. However, LMTs have also modulated tinnitus, something that suggests that they are able to provoke relevant excitation and sensitization of structures that are involved with detecting and processing nociceptive afferent stimuli.

Involvement of the autonomic nervous system may explain some of the findings regarding the effect of stimulation of MTPs on tinnitus. Increased sympathetic activity explains the autonomic symptoms associated with MTPs and provides a mechanism by which local injury and nociception causes local tension. According to Hubbard and Berkoff (1993), MTP spontaneous electromyography activity is generated from sympathetically stimulated intrafusal muscle fiber contractions, and not from extrafusal fibers.

An electron microscopy study in cats demonstrated sympathetic nerve endings in close proximity to intrafusal neuromuscular junctions and muscle fiber membranes (Santini and Ibata, 1971). In another study, Grassi et al. (1986) found that cervical sympathetic nerve stimulation in rabbits produced increases in jaw tension with intravenous injection of noradrenaline and phenylephrine. They also noticed that phenoxybenzamine inhibited the tension effect of sympathetic stimulation by approximately 50% and that the combination of this blocker and a selective alpha-2 blocker eliminated it.

Studies have found that the sympathetic input block to the ear or a sympathectomy can alleviate tinnitus in some patients (Wilmot, 1961; Golding-Wood, 1973; Adams and Wilmot, 1982).

Similarities between tinnitus and pain

There are many similarities between chronic tinnitus and chronic pain (Tonndorf, 1987; Møller,

1997, 2000; Folmer et al., 2001) (Chapter 4). Briner (1995) used the phrase “phantom auditory pain” to describe severe chronic tinnitus. Chronic pain causes central sensitization, neuroplasticity and dysfunction of the pain suppression system through expression of neural plasticity (Møller, 2006). The fact that both pain and tinnitus can be modulated by stimulation of MTPs is another similarity between tinnitus and pain that has not been reported earlier. Rocha (2005) found that individuals with tinnitus were more likely to complain of chronic pain in the head, neck and shoulder girdle (33%; OR = 2.81) when compared to the non tinnitus participants (14.9%). They found that complains about pain took place before or at the same time as of tinnitus in 64.5% of patients.

Camparis et al. (2005) observed that patients with sleep bruxism (clenching of the teeth) and tinnitus usually complained more of chronic facial pain than patients with sleep bruxism without tinnitus. The authors concluded that these findings support the hypothesis that tinnitus and myofascial pain are related. Other studies (Fricton et al., 1985) showed that 42.1% patients with myofascial

pain syndrome in the face and neck regions also had tinnitus and that 54.2% out of 72 patients with chronic pain also complained of tinnitus (Isaacson et al., 2003).

Treatment of tinnitus would therefore benefit from using similar methods as used in pain management and assessment of success would benefit from using methods common in pain research such as visual analog scales.

MTP evaluation

The criteria for the presence of both AMTPs or LMTPs are presence of a taut palpable muscular band with hypersensitive spots throughout this band, as well as referred pain with a pattern for each muscle. Palpation should be performed with sustained deep single-finger pressure during up to 10s with a spade-like pad at the end of the distal phalanx of the index finger or through pincer palpation (thumb and finger) moving across the muscle band at the hypersensitive area. The patient should be in a silent environment so as to facilitate perception of possible tinnitus

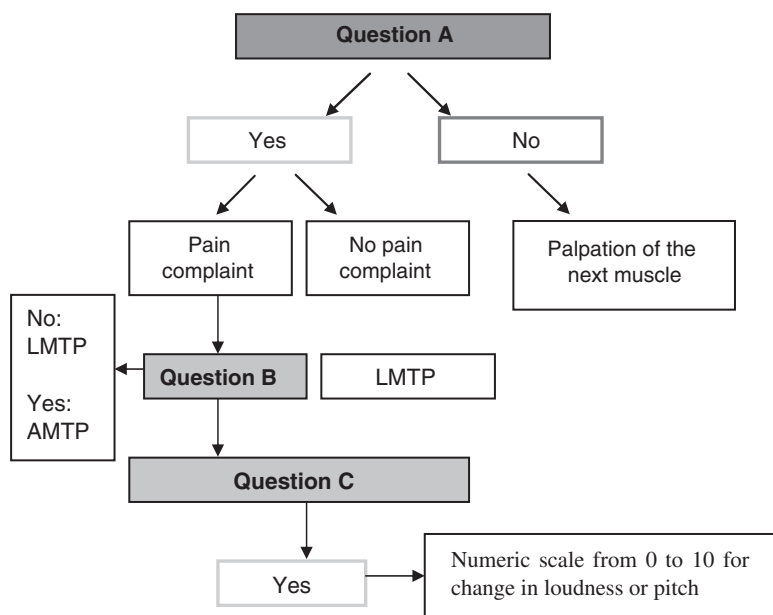


Fig. 1. Questions asked during MTP evaluation.

modulation upon MTP palpation. The nine muscles in the head, neck and shoulder girdle, infraspinatus, levator scapulae, trapezius, splenius capitis, scalenus medius, sternocleidomastoid, digastric, masseter and temporalis, should be examined for the presence of MTPs, according to Travell and Simons (1999). Modulation is considered present in cases of immediate increase or decrease of at least one point in the scale and/or changes in the type of sound. The patient should be asked questions according to the scheme shown in Fig. 1.

The localization of the MTPs from which tinnitus could be modulated should be noted if palpation of the MTPs modulated the intensity (up or down) if the character of the tinnitus changed and if the change occurred ipsilateral or contralateral to MTPs. Patients in whom the tinnitus can be modulated by MTP palpation or who present only myofascial pain complaint are candidates to specific pain treatment and MTP deactivation.

Conclusion

The observed similarities between tinnitus and myofascial pain confirms that the pathophysiology of tinnitus is complex and that tinnitus is not always caused by disorders of the ear. Patients with tinnitus should therefore be evaluated using complete examination of the head, neck and shoulder girdle musculoskeletal system by physicians who are trained in these examinations, which are necessary for arriving at a correct diagnosis and starting proper therapy.

Abbreviations

AMTP	active myofascial trigger point
LMTP	latent myofascial trigger point
MTP	myofascial trigger point

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CHAPTER 19

Assessment of temporomandibular and cervical spine disorders in tinnitus patients

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Abstract: In treating patients with temporomandibular joint (TMJ) dysfunction it was noticed that tinnitus and vertigo were common in such patients and there was also muscular tension in jaw and neck. During treatment of these patients it was also noted that injection of lidocaine in a jaw muscle (m. pt. lat.) reduced not only their muscular problems but also that the tinnitus was reduced while the local anesthetic was active. Evaluation of 39 patients with disabling tinnitus, and all suffered from tinnitus, revealed that 10 of them had bilateral tinnitus and TMJ disorders revealed that pain in the face, temples or jaw occurred often among these patients. Many of such patients had also symptoms of cervical spine disorders, head, neck and shoulder pain, and limitations in side bending and rotation were also frequent complaints. One-third of these patients could influence tinnitus by jaw movements and 75% could trigger vertigo by head or neck movements.

Treatment of jaw and neck disorders in 24 patients with Ménière's disease had a beneficial effect on not only their episodic vertigo but also on their tinnitus and aural fullness. At the 3-year follow-up, intensity of all symptoms were significantly reduced ($p < 0.001$).

Keywords: tinnitus; temporomandibular joint disorders; craniomandibular disorders

Introduction

It was observed many years ago that tinnitus might be related to dysfunction in facial joints and muscles. Thus Costen suggested temporomandibular joint (TMJ) disorders as a source of tinnitus (Costen, 1934), and House discussed muscular tension after a whiplash injury to be a possible cause of tinnitus (House, 1981). Relation between TMJ and tinnitus has been reported more recently (Morgan, 1992). Few studies of TMJ disorders that may affect the tinnitus in patients with Ménière's diseases have been published. This

chapter will discuss how various forms of tinnitus may be related to temporomandibular-craniomandibular disorders and how treatment of these disorders can alleviate tinnitus.

Results

When lidocaine was injected intramuscularly in the lateral pterygoid muscle on the tinnitus side in 39 patients, all 39 of the participants had disabling tinnitus — 10 had bilateral tinnitus. An average of 63% of the participants experienced relief after 3–5 min, according to a visual-analog scale. The tinnitus returned when the anesthetics wore off (Björne, 1993).

[†]Sadly Dr. A. Björne passed away before this volume was published

In a study, 24 patients with Ménière's disease were compared to a matched group of control participants selected from the population in the same area of Sweden (Björne and Agerberg, 1996). Both groups were screened for symptoms with a self-administered questionnaire and also evaluated by a routine stomatognathic examination. The function of the masticatory system was evaluated according to the Helkimo dysfunction index (Helkimo, 1974).

Clinical symptoms of TMJ disorders such as pain in the face or jaws, pain on movement of the mandible and fatigue of the jaw were more common in the Ménière's group ($p < 0.01$). Pain located in the vertex area, in the neck/shoulder area, and in the temples also occurred more often in the patient group ($p < 0.01$), and the frequency of tenderness to palpation of the masticatory muscles, the TMJ ($p < 0.001$) and the upper part of the trapezius muscle was also higher in the patient group than in the control group.

In a dental praxis it was noticed that many patients who had TMJ disorders also had tinnitus and symptoms from the cervical spine (cervical spine disorder, CSD), and it seemed like a natural step to also investigate the prevalence of CSD in the patient group from the TMJ study. In the CSD study, 24 of the patients with Ménière's disease participated, as did 24 of the matched control subjects from the population sample (Björne et al., 1998).

Symptoms of CSD, such as head and neck/shoulder pain ($p < 0.01$), and signs as limitations in side-bending and rotation movements were all significantly more frequent in the patient group than in the control group. Severe tenderness to palpation of one side of the transverse processes of the atlas and the axis ($p < 0.001$), the upper and middle trapezius ($p < 0.01$), and the levator scapulae muscle ($p < 0.01$) was also significantly more frequent in the patient group.

Most of the patients, 75%, reported that head and neck movements in the atlanto-occipital and atlanto-axial joints could trigger attacks of vertigo. Also, 29% of the patients could influence their tinnitus by mandibular movements.

In conclusion, the study showed a much higher prevalence of signs and symptoms of CSDs in

patients diagnosed with Ménière's disease compared to control subjects from the general population.

Ménière's disease

In a study where 24 patients with Ménière's disease received a coordinated treatment of TMJ and CSD, there were significant reductions in the severity of the TMJ symptoms first at the 1-year follow-up ($p < 0.01$). The reductions remained until the 3-year follow-up (Björne and Agerberg, 2003). The patients were 29–74 years (average 52 years) and had their symptoms from 1–27 years (average 8 years). The patients were followed for 3 years and examined every 6 months using self-administered questionnaires and visual-analog scales.

The reduction in intensity of Ménière's disease symptoms from the coordinated treatment was in most cases not significant at the first 6-month follow-up (C1), except for pain in neck and shoulders ($p < 0.05$). All symptoms were significantly reduced at the 1-year follow-up (C2); vertigo, dizziness, tinnitus, pain in face and jaws, pain in neck and shoulders ($p < 0.001$), headache ($p < 0.01$) and aural fullness ($p < 0.05$). At the 3-year follow-up (C6), the intensity of all symptoms was reduced with high significance ($p < 0.001$) (Fig. 1).

Significant longitudinal reductions were also reported in the frequencies of the occurrence of vertigo and non-whirling dizziness (Fig. 2).

A reduction in the frequency of headache was reported by the patients ($p < 0.05$), as well as a complete disappearance of pain located in the vertex area ($p < 0.01$) in the nine patients that reported it at the initial examination.

There were no changes in the patients' estimation (visual-analog scale) of how comfortable they felt in work, studies, or home life, but their mood of nervousness improved from 3.7 to 1.8 during the 3-year follow-up ($p < 0.01$).

In conclusion, the results showed that a coordinated treatment of TMJ and CSD in patients with Ménière's disease was an effective therapy for symptoms of this disease. The results also suggested that Ménière's disease has a clear association with TMJ and CSD and that these three

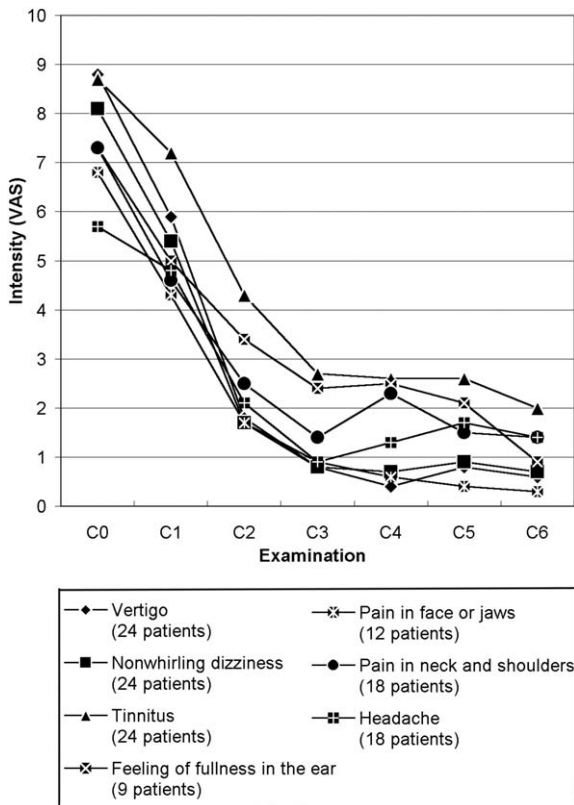
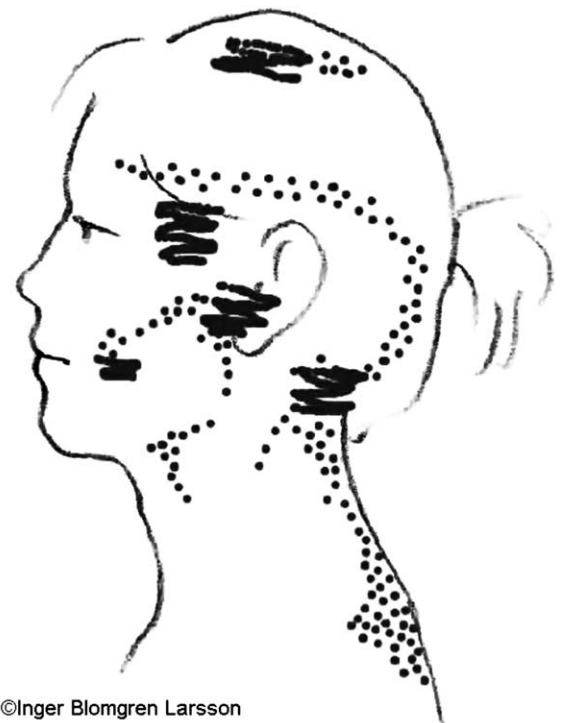


Fig. 1. Intensity of symptoms assessed using a visual-analogue scale in 24 patients with Ménière's disease at baseline (C0) and at the six half-year follow-ups (C1–C6) after coordinated treatment of temporomandibular and cervical spine disorders.



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Fig. 3. A common pattern of pain for patients with tinnitus, vertigo and Ménière's disease, which indicates that jaw and neck can be considered as an integrated sensory system.

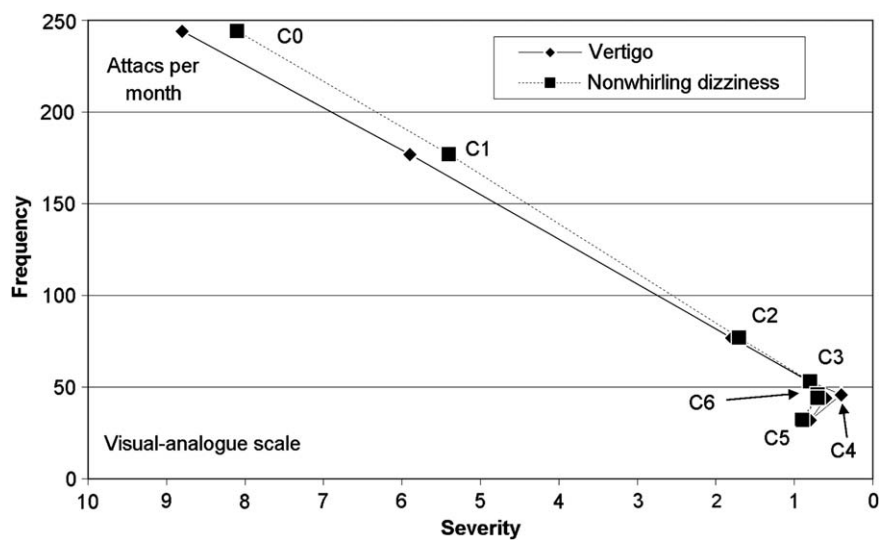


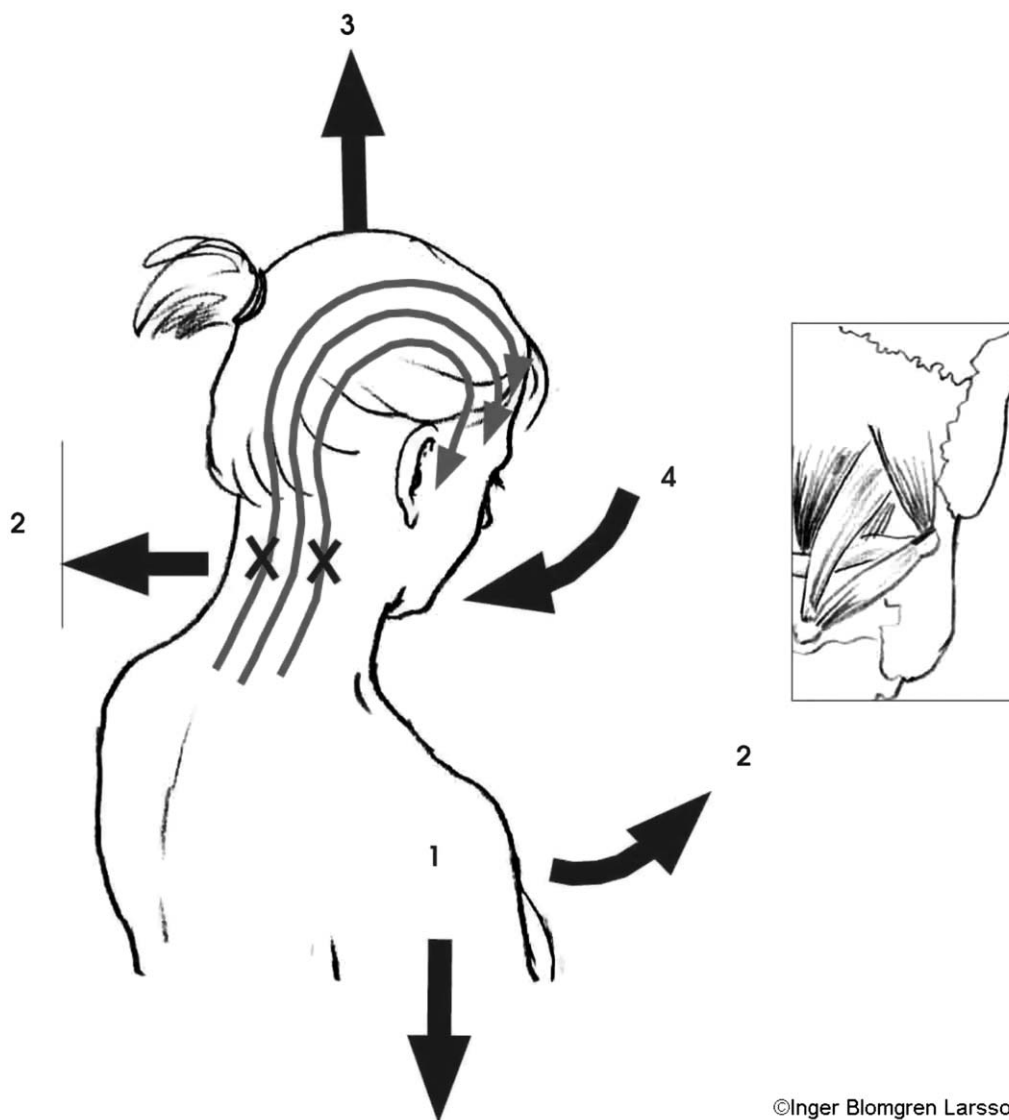
Fig. 2. Frequency related to severity of vertigo and non-whirling dizziness in 24 patients with Ménière's disease at baseline (C0) and at the six half-year follow-ups (C1–C6) during the 3-year follow-up after coordinated treatment of temporomandibular and cervical spine disorders.

ailments appeared to be caused by the same stress, nervousness and muscular tension (See Fig. 3).

Relaxation and posture

The aim of the treatment is to reduce muscular tension in jaw and neck. The patient is ordered a

stretching exercise of the suboccipital muscles, which the patient is asked to do frequently (See Fig. 4). At the end of the stretching exercise he is also asked to perform rotation movements in the atlanto-occipital joint, especially to the restricted side. The homework also includes relaxing exercises involving breathing with the diaphragm.



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Fig. 4. Stretching exercise for the sub-occipital muscles. (1) Lower your shoulders, breathe with diaphragm. (2) Move head/neck towards vertical line, raise your chest. (3) Raise your head lightly towards the ceiling. (4) Pull in the jaw and feel the stretch in the neck, slightly below the skull base. Repeat several times a day, especially if you experience vertigo. Stretch for 30s each time, and end the exercise by turning head gently left and right.

About 25% of the patients are referred to a physiotherapist for further treatment of the tension in the neck and for training in relaxing and normalizing posture.

Stress evaluation

Many patients' tinnitus debuted during a life crisis with stress and depression, which they are often still not through. Since 2003, these patients receive stress therapy as complementary treatment. The Stress Profile TM questionnaire (Setterlind and Larson, 1995) (Stress Management Center <http://www.smcenter.se/smce/index.html> 13 Jan 2007) is used to support life situation discussions with patients.

The therapist may help with guidance and support, and with correcting measures for dental occlusion and posture, but the condition for success is to a large extent in the hands of the patient.

A patient would have somatic tinnitus if he is able to alter the tinnitus sound, both sound level and pitch, by:

- performing movements of jaw, neck and eyes;
- tensing jaw, neck and face muscles but without movements (biting teeth together, pressing tongue etc);
- putting pressure with a fingertip on the temple, mandible, cheek, tragus, behind the ear and in the neck.

Abbreviations

CSD	cervical spine disorder
TMJ	temporomandibular joint

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CHAPTER 20

Tinnitus severity, depression, and the big five personality traits

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Abstract: A growing number of self-report measures for the evaluation of tinnitus severity has become available to research and clinical practice. This has led to an increased awareness of depression and personality as predictors of tinnitus severity in addition to loudness and other psychoacoustic measures. However, the net impact of personality dimensions on tinnitus ratings has not been investigated when the effect of depressed mood is controlled. In the present study, we demonstrate the role of the big five personality traits, ‘Neuroticism’, ‘Extraversion’, ‘Openness’, ‘Agreeableness’, and ‘Conscientiousness’, in affecting scores on two standard instruments for grading tinnitus-related complaints, the tinnitus handicap inventory (THI), and the tinnitus questionnaire (TQ). When 72 individuals with chronic tinnitus were examined, ‘Agreeableness’ negatively correlated with THI scores ($p = .003$), whereas the anxiety trait ‘Neuroticism’ correlated both with depressive symptomatology ($p < .001$) and TQ scores ($p = .028$), but not with THI ratings (n.s.). In addition to confirming the established roles of trait anxiety and depression, low ‘Agreeableness’ was thus identified as a novel predictor of tinnitus severity on the THI.

Keywords: tinnitus; big five personality traits; predictors; affective comorbidity; coping

Introduction

The interplay of personality traits, depressed mood, and tinnitus severity is highly relevant to diagnosis and prognosis in tinnitus-related handicap (Russo et al., 1994). Depression often occurs together with tinnitus (Harrop-Griffiths et al., 1987) and frequently augments functional disability in individuals with tinnitus (Sullivan et al., 1993). In the light of strong placebo effects in tinnitus (Dobie et al., 1993), psychological factors play a further modulatory role in shaping the

perception and report of distress associated with tinnitus. Close collaborations between audiologists and mental health professionals have been established in many specialized clinics to meet the specific challenges posed by these interactions (Reynolds et al., 2004).

Among the personality traits that have been identified in the past as predictors of subjective tinnitus severity counts self-reported anxiety (Halford and Anderson, 1991; Langenbach et al., 2005). Measures of anxiety sensitivity, or of excessive pre-occupation with somatic symptoms are often used in combination with tools addressing depression to adequately assess the severity of tinnitus at initial screenings, and to evaluate treatment outcome (Reynolds et al., 2004). Except for

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the contributory roles of depression and anxiety, however, little is known about personality-specific risk factors. Likewise, little is known about the relationship between temperament, self-reported depression and other forms of tinnitus-related handicap (Zachariae et al., 2000). There is preliminary evidence that the respective measures are not independent of each other and that symptom severity scales may give skewed results when personality traits and affective states are not controlled for (Langenbach et al., 2005). In order to further improve our understanding of factors that may augment, or reduce, the morbidity associated with chronic tinnitus we therefore compared the outcome of two widely used tinnitus severity scales in relation to the severity of depression and individuals' temperament. To this avail, we studied 72 individuals suffering from chronic tinnitus who were administered the tinnitus handicap inventory (THI; Newman et al., 1998; Kleinjung et al., 2007), the tinnitus questionnaire (TQ; Hallam et al., 1988; Goebel and Hiller, 1994), the Beck depression inventory (BDI; Beck et al., 1988), and the NEO-five factor inventory (NEO-FFI; Costa and McCrae, 1985). Partial correlations were computed of NEO-FFI subscales with the BDI, TQs, age, and gender.

Methods

One hundred patients who had presented consecutively to the university tinnitus clinic in the months preceding February 2005 were enrolled in the study. All had reported tinnitus as their primary complaint at the time of their audiologic examination, and had undergone a neurootological examination including otoscopy, recording of the acoustic middle ear reflexes, tympanometry (middle ear pressure measurements), pure tone audiometry, and tinnitus pitch and loudness matching. Questionnaires were administered by mail with a stamped return envelope and an accompanying letter providing instructions on how to fill out the NEO-FFI, BDI, THI, and TQ. Where required, demographic data (age, sex, and history length) and descriptive data about the tinnitus were reconfirmed by telephone interviews

to supplement the subjects' medical records. Seventy-two of the 100 individuals who were enrolled in the study returned fully completed sets of questionnaires. Of these, 50 participants were men (mean age 49.3 ± 13.0 years, range: 19–75) and 22 were women (mean age 49.4 ± 13.1 years, range: 23–73). All participants complained of chronic tinnitus. The age at onset of tinnitus was 43.1 ± 12.6 years (range: 17.5–66.5) in men, and 43.2 ± 13.1 years (range: 21–65) in women. All participants had experienced tinnitus for at least 6 months; 25 individuals (34.7%) reported tinnitus persisting for more than 5 years.

Descriptive statistics, normality tests, and partial correlations were calculated using STATA for Macintosh V8.0 (Stata Corporation, College Station, TX, USA). Means are given with the respective standard deviation. The significance level was set at $p = .05$.

Results

Table 1 shows the total scores on the THI and TQ, together with results of distribution analyses. Both measures of severity followed a Gaussian distribution ($p > .22$). Using the consensus grading scheme of tinnitus severity from 'slight' to 'catastrophic' on the THI (McCombe et al., 2001), 13 participants (18.1%) reported grade I (slight) tinnitus, 1 individual only displayed symptoms on the TQ, 17 patients (23.0%) had grade II (mild), 22 participants (30.1%) scored as grade III (moderate) sufferers, 17 (23.6%) reported grade IV

Table 1. Mean scores \pm S.D. and Shapiro–Wilk normality test results for measures of five personality traits (NEO-FFI), depressive symptomatology (BDI), and tinnitus severity (THI, TQ)

	Mean	z	p
Neuroticism	1.80 ± 0.68	0.11	0.46
Extraversion	2.13 ± 0.57	0.02	0.49
Openness	2.25 ± 0.43	–1.10	0.86
Agreeableness	2.50 ± 0.38	–0.84	0.80
Conscientiousness	2.89 ± 0.50	–0.72	0.76
BDI	11.00 ± 9.48	3.70	<0.01
THI	40.30 ± 24.11	0.75	0.23
TQ	43.32 ± 20.15	0.75	0.23

(severe) handicap, and 3 patients (4.2%) scored as grade V. With respect to depression, 20.8% of subjects exhibited moderate to severe symptoms (defined as a score >19 on the BDI scale, Beck et al., 1988), and 34.7% presented with mild depressive symptoms (defined as a score of 10–18). Distribution of BDI scores deviated from normality ($p < .01$, see Table 1 for mean values and Shapiro–Wilk statistics). As regards personality dimensions, participants in the study scored highest on ‘Conscientiousness’ (2.89 ± 0.50), and lowest on ‘Neuroticism’ (1.80 ± 0.68). All NEO-FFI scores displayed a normal distribution (Table 1).

Correlation analysis revealed that low ‘Agreeableness’ predicted high THI scores ($p = .003$) whereas high ‘Neuroticism’ predicted high TQ scores ($p = .028$, Table 2). All partial correlations are displayed in Table 2.

Discussion

This is the first study to identify low ‘Agreeableness’ as a personality dimension highly correlated with tinnitus severity. Individuals who score low on ‘Agreeableness’ are thought to be highly

competitive, self-centered, and more susceptible to anger (Meier and Robinson, 2004). It is conceivable that such individuals experience more discomfort from tinnitus compared to others, owing to a perceived inability to meet their own expectations and the levels of performance that they are used to achieve in everyday challenges. This may result in frustration, feelings of tenseness and irritability (Sourgen and Ross, 1998), and may increase the handicap from tinnitus. If a causative relationship between low ‘Agreeableness’ and tinnitus severity can be confirmed, predictors of tinnitus severity may overlap with personality profiles of individuals who carry an increased risk of coronary heart disease.

It has been noted that cardiovascular complaints are frequent in individuals with tinnitus (Hiller et al., 1997), and behavioral risk factors for coronary diseases have been suggested to promote chronic tinnitus (Stobik et al., 2005).

When severity was assessed by the TQ, ‘Neuroticism’ was identified as the only significant personality correlate ($p = .028$, Table 2). Individuals who score high on ‘Neuroticism’ tend to experience more anxiety, fear, sadness, embarrassment, and guilt. There is consensus that anxiety is

Table 2. Partial correlations between scales and demographic variables in subjects with chronic tinnitus ($N = 72$)

	N	E	O	A	C	BDI	Sex	Age	THI	TQ
Neuroticism (N)		–.353 [.004]	–.078 [.545]	–.112 [.378]	–.130 [.305]	.472 [.000]	–.252 [.045]	–.282 [.024]	.017 [.892]	.276 [.028]
Extraversion (E)			–.080 [.529]	.065 [.609]	.175 [.167]	–.089 [.483]	–.036 [.779]	–.351 [.004]	.054 [.671]	.106 [.404]
Openness (O)				.192 [.129]	–.104 [.414]	–.003 [.981]	–.029 [.823]	–.047 [.715]	.167 [.188]	–.066 [.607]
Agreeableness (A)					.293 [.019]	.035 [.782]	–.156 [.219]	.003 [.979]	–.367 [.003]	.197 [.119]
Conscientiousness (C)						–.104 [.414]	–.037 [.772]	.075 [.554]	.222 [.078]	–.087 [.496]
BDI							.069 [.589]	.045 [.727]	.248 [.048]	.057 [.655]
Sex								–.063 [.624]	–.052 [.686]	.106 [.406]
Age									–.186 [.142]	.357 [.004]
THI										.560 [.000]
TQ										

Note: Significant correlations are printed in bold, p values are given in square brackets.

prevalent in subjects with tinnitus when measured as a state (Reynolds et al., 2004) or, as a trait (Hiller and Goebel, 2004). However, studies using more than one index of anxiety suggest correlations with traits are weaker than those with anxiety states (Andersson et al., 2003). This could explain why no significant correlation of 'Neuroticism' was seen with the THI score or, with TQ subscales (data not shown). Alternatively, the TQ and THI may differ in their sensitivity to different facets of trait anxiety as have been proposed by Endler and Kocovski (2001).

The present study is also the first systematic study of personality traits in subjects with tinnitus using the NEO-FFI. Previously, investigators have employed Cloninger's tridimensional personality questionnaire (TPQ) (Russo et al., 1994), the Freiburger personality inventory (FPI-R), the symptom checklist-90-revised (SCL-90-R) (Sullivan et al., 1993; Langenbach et al., 2005), the Minnesota multiphasic personality inventory (MMPI) (Collet et al., 1990), or the Eysenck personality inventory (EPQ) (Zachariae et al., 2000). In contrast to the MMPI and the EPQ, the NEO-FFI has no scales to control for response biases such as social desirability or faking bad. Data obtained with the MMPI, however, argue against intentional bias in populations affected by tinnitus (Bayar et al., 2002; Marciano et al., 2003).

As for the strong correlations between the trait 'Neuroticism', female gender ($p = .045$), and age (negative correlation, $p = .024$), others have shown that a decrease in 'Neuroticism' with age, especially in women, occurs independently of tinnitus when large cohorts are studied from the general population (Srivastava et al., 2003).

A significant correlation of tinnitus severity was equally noted with depression. Depression is common in individuals with chronic tinnitus (Zoger et al., 2001), which may indicate that individuals with tinnitus have poor compensation strategies, or a predisposition for both conditions. Negative effects of depression on coping behaviors may manifest as nonhabituation to tinnitus symptoms (Reynolds et al., 2004), and a reduced drive to seek medical attention. At the same time, depression occurring together with tinnitus may render some interventions for tinnitus less effective, e.g. the

practice of cognitive behavioral therapy. A major emerging risk factor for depressive comorbidity is internal focus (Newman et al., 1997). Hallam et al. (1988) first postulated that attentional processes akin to obsessional ruminations play a key role in modulating the perceived handicap from tinnitus. Others have confirmed the joint contribution of depression, somatic perception, and temperament to the psychological strain defining the handicap from tinnitus (Perrig-Chiello and Gusset, 1996).

Conclusions

Significant correlations have emerged among the severity of tinnitus, depression, and two dimensions of personality. Tinnitus severity was predicted by low 'Agreeableness' and high 'Neuroticism', but the degree of correlation depended on which measure of severity was used. It remains to be seen whether the unhappy triad "depression, anxiety/'Neuroticism' and irritability/low 'Agreeableness'" is an indicator of somatic comorbidity that may warrant adaptations of interventional techniques in individuals with chronic tinnitus.

Abbreviations

BDI	Beck depression inventory
NEO FFI	NEO-five factor inventory
THI	tinnitus handicap inventory
TQ	tinnitus questionnaire

Acknowledgments

The authors wish to thank Sandra Pfluegl and Helene Niebling for assistance with data collection. The study was supported by a grant from the Tinnitus Research Initiative.

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CHAPTER 21

Tinnitus and insomnia

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Abstract: Sleep problems are common in individuals with tinnitus but it is not known if they can be seen as a reaction to the acoustic percept of tinnitus disturbing normal sleep, or if there are common causes. Sleep problems further impair the quality of life of individuals with tinnitus and the impairment correlates with the severity of the tinnitus. However the nature of the relationship between tinnitus and disturbed sleep in individuals with tinnitus is not clearly understood. Preliminary studies suggest that chronically disturbed sleep (insomnia) in individuals with tinnitus that is not caused by organic disorders exists unrelated to the tinnitus. We studied the relationship between tinnitus and insomnia in a retrospective sleep study of 13 hospitalized patients with insomnia and tinnitus. Patients with sleep apnea, periodic leg movements, or a severe psychiatric disorder were excluded. We collected physiologic sleep measures (EEG, EOG, EMG, and respiration) and subjective sleep information from a morning protocol during two nights. We also obtained information about performance in sustained attention tasks and the scores of self-rated depression scale and self-rated daytime-tiredness scale. Thirteen age- and sex-matched inpatients with primary insomnia who did not have tinnitus served as controls. There were no significant differences between the physiologic data obtained in patients with tinnitus and in the controls. Both groups had low sleep efficiency but the patients with both insomnia and tinnitus had longer subjective sleep latencies than insomnia patients without tinnitus (controls). No differences were found in sustained attention tasks, subjective daytime tiredness, and depression rating scores between the two groups. Similarities between the results from these two groups suggest that sleep specific psychotherapeutic methods, which are established for treating insomnia, should be further developed for the use in patients with insomnia and tinnitus.

Keywords: tinnitus; insomnia; sleep; psychotherapy; polysomnography

Introduction

“I could deal with tinnitus alone but not with the disturbed sleep.” This statement made by one of our patients highlights the particular problem of individuals with tinnitus and sleep problems, namely that coping with tinnitus is impaired by

disturbed sleep. Sleep problems are a frequent complaint by patients with tinnitus (Tyler and Baker, 1983; Jakes et al., 1985) with a prevalence ranging from 50% (Hallam, 1996) to 77% (Alster et al., 1993). Insomnia has been reported to be associated with greater perceived loudness of tinnitus (Folmer and Griest, 2000) and tinnitus is perceived to be more severe in combination with disturbed sleep (Meikle et al., 1984; Alster et al., 1993).

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Characteristics of sleep in individuals with tinnitus

It has been shown that subjective sleep of individuals with tinnitus is characterized by increased sleep onset latency (SOL), increased midsleep and morning awakening (Alster et al., 1993), and reduced total sleep time (TST) (Hallam, 1996); sleep quality is impaired and subjective sleep efficiency (SEFF) is low (Burgos et al., 2005).

Polysomnographic data (physiologic measures of sleep, which includes electroencephalography (EEG), electrooculogram (EOG), and electromyography (EMG)) show that both tinnitus patients with a complaint of disturbed sleep and patients with insomnia but no tinnitus have a shorter sleep compared with that in healthy controls (Burgos et al., 2005). To further investigate whether sleep patterns in individuals with tinnitus and insomnia are different from those in insomnia patients without tinnitus (INS), we examined data from our sleep laboratory in a retrospective study.

Retrospective study of sleep of insomnia patients with tinnitus in comparison to insomnia patients without tinnitus

We compared data of patients with insomnia who had tinnitus with those of insomnia patients without tinnitus. Specifically we studied the differences in polysomnographic and subjective sleep data, results of sustained attention tasks, self-rated depression, and self-rated daytime tiredness in these two types of patients.

Methods and patient selection

Thirteen individuals with insomnia who were treated as inpatients and who had tinnitus (TIN) participated in the study. The patients underwent two nights with polysomnography in our sleep laboratory and filled out a morning questionnaire on subjective sleep (morning protocol, MP). Patients with sleep apnea, periodic leg movements, any other organic sleep disorder or any severe psychiatric disorder were excluded. Thirteen sex- and age-matched inpatients with primary insomnia served as a control group in the study

(INS). Both groups consisted of five women and eight men. The mean age for the patients with insomnia and tinnitus (TIN group) was 50.08 (SD = ± 12.63 years) and 51.92 years (SD = ± 11.73 years) for the INS group.

Polysomnographic recordings were performed according to the standards of the German Sleep Society with the patient lying in a comfortable bed in a sound attenuated room with EEG, EMG, and EOG recordings and staged according to the criteria of Rechtschaffen and Kales (1968). Respiration and leg movements were also recorded. Recorded sleep variables were SOL (time from lights out to the first epoch of stage 2), total sleep time (TST), sleep period time (SPT; time from sleep onset until final awakening), SEFF (TST/Time in bed (%)), and wake time after sleep onset (WASO). Duration of sleep stages 1–4 and rapid eye movement (REM)-sleep were expressed as percentage of SPT. Subjective sleep onset latency (SUBSOL) and subjective total sleep time (SUBTST) were obtained from MP.

Psychometric data of self-rated daytime tiredness (ESS, Johns, 1991) were collected. Epworth Sleepiness Scale (ESS) is a standard instrument for measuring subjective sleep propensity during the day (cut off = 10 points). For measuring depressiveness the Beck Depression Inventory (BDI) score (Beck and Steer, 1984; Hautzinger et al., 1994) was used. Sustained attention was measured with a 25 min computer-based test (Macworth Clock Version, Quatember Maly, QM, Schuhfried, 1993). From QM mean reaction time (RT), number of missed reactions (NUMMR) and number of false reactions (NUMFR) were calculated for each person.

Statistics

For all sleep parameters (subjective and objective) the average values over two nights were used. Student's *t*-test was used in analysis of the subjective and objective sleep parameters and for sustained attention test parameters; Mann Whitney U-test was used to compare BDI scores and ESS scores of the two groups. Level of significance was set to $p < .05$. Alpha adjustment was

not applied due to the exploratory nature of the study.

Results

Mean objective sleep latency was 21.46 ± 10.06 min for INS and 35.50 ± 25.41 min for TIN (t -test: n.s., Fig. 1). TIN reported longer SUBSOL ($69.54 \text{ min.} \pm 37.72 \text{ min}$) than INS (SUBSOL: $22.80 \pm 21.65 \text{ min}$) (t -test: $T = -2.429$; $p = .025$). There were no significant differences between the INS and the TIN group regarding objective or subjective sleep time (Table 1) or any other sleep parameter, such as WASO, TST, SPT, percentages of sleep stages (1, 2, 3, and 4 and REM-sleep), and SEFF. SEFF was low for both groups (83.12% for INS and 80.81% for TIN). ESS scores, sustained attention test (QM) results, and BDI scores in both groups were within the normal range and no significant differences between TIN and INS were found (Table 2).

Discussion

The present study showed that objective sleep measurements do not differ between TIN and those with insomnia alone. Both groups had low SEFF and long SOL. These results are in line with recent data (Burgos et al., 2005). Our study also showed that the subjective sleep latency was longer in the tinnitus patients than the control group. This could be due to the sound percept in tinnitus patients: insomnia patients often give proof for waking time during the night with “every tiny sound they could hear” or remembered clock time. Insomnia patients therefore proof perceived wake time at night with sensory experiences (such as noises they have heard or looking at their watch). In addition monitoring the clock when trying to get to sleep triggers pre sleep worrying and misperception of sleep (Tang et al., 2007). Tinnitus during sleep onset may represent a comparable stimulus that influences sleep perception with a bias for remembered wake time.

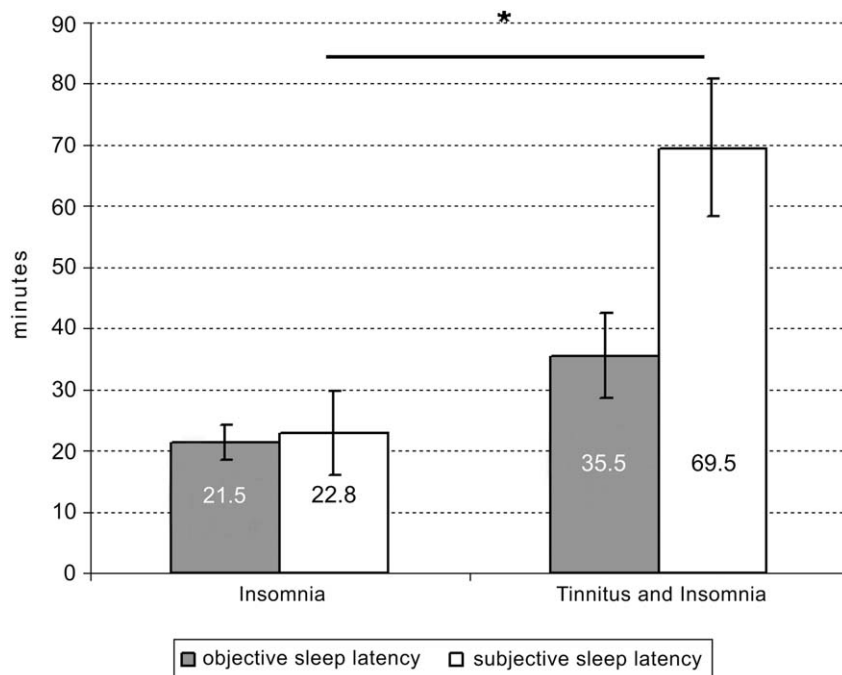


Fig. 1. Mean objective and subjective sleep latencies (and standard error of the mean) over two nights of 13 insomnia patients with tinnitus and 13 age- and sex-matched insomnia patients. * = $p < .05$, t -test.

Table 1. Subjective and objective total sleep time and other objective sleep parameters of insomnia patients (INS) and insomnia patients with tinnitus (TIN)

	INS	TIN	<i>t</i> -test
Subjective total sleep time (min)	353.89 ± 105.44	290.83 ± 95.29	n.s.
Total sleep time (min)	387.27 ± 46.80	368.46 ± 63.44	n.s.
Sleep period time (min)	444.08 ± 32.31	425.54 ± 49.66	n.s.
Wake after sleep onset (min)	74.54 ± 56.17	56.15 ± 17.51	n.s.
Sleep efficiency (%)	83.12 ± 5.32	80.81 ± 10.70	n.s.
Stage 1 (percentage of SPT)	18.13 ± 9.22	14.61 ± 7.61	n.s.
Stage 2 (percentage of SPT)	42.0 ± 10.07	45.33 ± 10.30	n.s.
Stage 3 (percentage of SPT)	8.34 ± 6.82	5.79 ± 5.81	n.s.
Stage 4 (percentage of SPT)	0.95 ± 2.69	1.60 ± 3.55	n.s.
REM-sleep (percentage of SPT)	16.97 ± 3.79	17.45 ± 4.40	n.s.

Note: Mean and standard deviation.

Table 2. Parameters of vigilance test (Quatember Maly), Epworth sleepiness scale (ESS), and Beck depression inventory (BDI)

	INS	TIN	<i>t</i> -test and Mann Whitney U-test
Sustaining attention task (Quatember Maly)			
Missed reactions	1.91 ± 2.84	3.33 ± 6.08	n.s.
False reactions	2.09 ± 2.26	0.58 ± 1.16	n.s.
Mean reaction time (s)	0.45 ± 0.05	0.53 ± 0.11	n.s.
Daytime sleepiness			
ESS score	7.92 ± 4.48	5.75 ± 5.06	n.s.
Depression			
BDI score	9.91 ± 6.65	11.88 ± 7.92	n.s.

No differences could be found in subjective ratings of daytime sleepiness (ESS) or depression (BDI). Both are within normal range. This is in accordance with the assumption that sleep problems of individuals with tinnitus are not a symptom of a depressive disorder (Hallam, 1996), although some data indicate a higher degree of depression in tinnitus patients with insomnia (Alster et al., 1993) as well as in insomnia (Coursey et al., 1975; Taylor et al., 2005).

Results of test of sustained attention performance (QM), which is sensitive to effects of sleep deprivation, were within the normal range for both groups. This result is in line with earlier studies in insomnia patients who demonstrated unimpaired attention performance as compared to healthy controls (Mendelson et al., 1984; Bonnet and Arand, 1995). Being alert in spite of bad sleep is explained with a physiological hyperarousal in insomnia patients (Bonnet and Arand, 2003). Our finding that sustained attention performance did

not differ between the two groups, further supports the hypothesis that the pathophysiology of insomnia is similar in patients with and without tinnitus.

Therapy of tinnitus and sleep disorder

It has been shown that many patients with tinnitus and disturbed sleep have organic causes such as apnea or periodic leg movements. Thus investigating 26 patients with tinnitus and disturbed sleep, Eysel-Gosepath and Selivanova (2005) found 10 with obstructive sleep apnea and 3 with periodic leg movements. This corresponds to our own clinical experience of a high prevalence of organic sleep disorders in tinnitus patients with sleep problems. Diagnosis of organic sleep disorders is highly relevant, since cause oriented treatment methods are available. However it has not yet been investigated whether specific treatments for organic

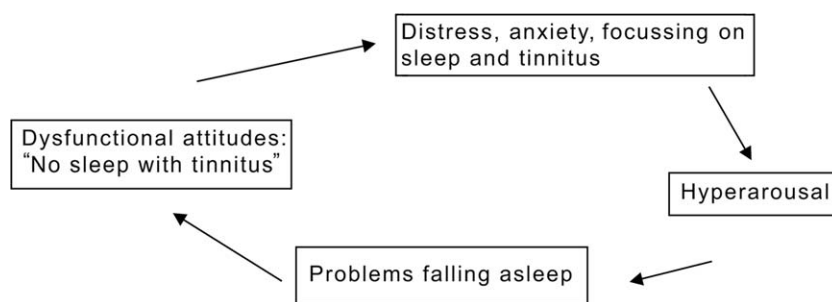


Fig. 2. Cognitive model of maintaining factors of tinnitus and insomnia.

sleep disorders such as continuous positive airway pressure (CPAP) treatment of sleep apnea may have a beneficial effect on co-occurring tinnitus in such patients.

Many patients with tinnitus and disturbed sleep are receiving sleep-inducing drugs such as benzodiazepines or antidepressants. There are some indications that benzodiazepines can improve tinnitus (Dobie, 1999) and that melatonin may be beneficial regarding both tinnitus and sleep (Rosenberg et al., 1998; Megwalu et al., 2006). However the efficacy of drugs for the treatment of tinnitus and insomnia is limited and due to habituation, most sedative drugs are effective only for a limited amount of time.

Cognitive behavior therapy has been shown to have a positive and long lasting effect on primary insomnia (Edinger et al., 2001a, b; Morgenthaler et al., 2006; Morin et al., 2006). This approach is based on the assumption that insomnia is maintained by dysfunctional beliefs (Edinger et al., 2001b) and an attentional bias (Espie et al., 2006), which interact with dysfunctional behavior (for example prolonged time spent in bed) creating a vicious circle, which leads to permanent distress. Dysfunctional attitudes and anxious emotional involvement also play a role in management of tinnitus and can impair rehabilitation (Erlandsson et al., 1992; McKee and Stephens, 1992; Attias et al., 1995; Olderog et al., 2004). In addition to sleep disturbance, tinnitus is often associated with emotional distress and hearing problems (Hallam et al., 1988) and tinnitus may reduce the ability to participate in social life during the day and to recover during sleep at night. Similarities in psychopathology between tinnitus and insomnia

suggest that a model of a vicious circle with dysfunctional attitudes, anxiousness, and hyperarousal that can maintain insomnia (see Fig. 2) is also valid in describing the problems for individuals who have both tinnitus and disturbed sleep. Attributing sleep problems to patients' tinnitus may cause negative expectations and worries about sleep and may contribute to the development of insomnia.

Case report of tinnitus and insomnia

A woman 30-years-old with academic reputation working as a teacher. Since she always had a light sleep she instructed her husband to be as quiet as possible around bedtime and used earpieces at night. After being robbed one night she developed an acute hearing loss and a tinnitus. From this moment on she could not sleep anymore. She attributed her sleeping problems solely to the tinnitus and tried every therapeutic offer to get rid of it, without success. Her greatest fear was not being able to work again because of her sleeping disorders. Although disliking any kind of medication she regularly used hypnotics that supported her self-perception of being severely ill. After several stays in psychosomatic hospitals she was introduced in our sleep disorders center. Her attitude in the beginning was demanding and hopeless at the same time. Although she assured having read everything about sleep therapy, sleep specific psychotherapeutic methods were administered. During the therapy she realized that she could regain control over her sleep disorder by altering dysfunctional behavior concerning sleep.

Conclusion

The facts that (1) we did not find a difference between objective parameters of sleep in insomnia patients with and without tinnitus and (2) similar psychological mechanisms seem to be involved in both groups suggest that the development of specific cognitive behavioral therapy programs might be a promising approach for treatment of patients with tinnitus and insomnia. Success for treatment, however, will depend on whether the patients can accept that their tinnitus is not a specific sleep antagonist (McKenna and Daniel, 2005).

Abbreviations

BDI	Beck Depression Inventory
EEG	electroencephalography
EMG	electromyography
EOG	electrooculogram
ESS	Epworth sleepiness scale
INS	insomnia patients without tinnitus
MP	morning protocol
NUMFR	number of false reactions (in sustained attention test)
NUMMR	number of missed reaction (in sustained attention test)
QM	Quatember Maly, test for sustained attention
REM	rapid eye movement
RT	reaction time (in sustained attention task)
SD	standard deviation
SEFF	sleep efficiency
SOL	sleep onset latency
SPT	sleep period time
SUBSOL	subjective SOL
SUBTST	subjective sleep time
TIN	patients with insomnia and tinnitus
TST	total sleep time
WASO	wake time after sleep onset

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CHAPTER 22

Tinnitus treatment – state of the art

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Abstract: Clinical and scientific research has opened up a wide range of options for treating patients with tinnitus. Many of these options are sophisticated and are delivered through specialist tinnitus clinics. However tinnitus is a very common complaint. Most patients with tinnitus need to be satisfactorily cared for by front line clinicians. This chapter describes how one clinician who has looked after some thousands of patients with tinnitus looks after them now. It describes the model I use to explain tinnitus to the patient and develop a management plan. It describes how I assess patients with tinnitus. It lists the treatment options available. It describes the management provided at the first (and usually only) encounter. It stresses the value of a written report. It describes further management and onward referral. It describes my use of drugs in those patients for whom the tinnitus remains overwhelming.

Keywords: tinnitus; model; assessment; treatment; drugs

Introduction

Tinnitus is very common. In any one year a busy otologist or audiologist will see many, perhaps hundreds of new patients for whom the primary concern is tinnitus. Therefore we each need to have a plan for assessing and managing most of these patients effectively and expeditiously. There will be a proportion for which our management is inadequate. Provided this proportion is not too large then we can arrange for these remaining patients to receive the benefit of referral to a sophisticated but expensive and time-consuming program. This paper describes how I have managed several thousand patients with tinnitus over the last 30 years. I am delighted by the increased number of treatments now available to help me and the additional treatments available at the clinics to whom I refer those patients for whom my interventions are inadequate (Table 1).

Thirty years ago an anesthesiologist and I studied tinnitus sufferers by using questionnaires, general medical assessment, ENT assessment, neck and jaw assessment, audiometry and intravenous lidocaine (Melding et al., 1978; Goodey, 1987). Differing responses to lidocaine made it clear that there were different categories of tinnitus. Subsequently we attempted to correlate differing responses to lidocaine

Table 1. Treatment options available to help the clinician in managing a patient's tinnitus

Correct causes
Cognitive counseling
Improve “normal” auditory input
Reduce aggravating and non-auditory factors
Disassociate emotional factors
Treat depression
Treat generators medically with drugs
Sound therapy
Centrally acting drugs
Magnetic and/or electrical stimulation
Other tinnitus coping strategies
Holistic support groups

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with therapeutic trials of the anticonvulsants carbamazepine and phenytoin (Melding and Goodey, 1979). We developed a complex tinnitus model incorporating peripheral and central influences.

Clinicians need a tinnitus model on which to base their own understanding, their explanations and a management plan. For some patients a very simple model may still be sufficient. However a simple model is not adequate for those patients who need or may come to need more sophisticated management. The model we use needs to provide a framework within which we can categorize the tinnitus of different patients and identify potential sites for therapeutic intervention. Not only must it allow us to “grow” our explanation when more complex intervention is needed but it is also therapeutically helpful if we can use it to explain to patients the research, which is occurring and potential future developments.

In 1981 tinnitus was defined as “the sensation of sound not brought about by simultaneously applied mechano-acoustic or electrical signals” (Evered and Lawrenson, 1981). We specifically excluded objective tinnitus or “somatosounds”. However the intrusiveness of such somatosounds is increased by much the same processes as the intrusiveness of subjective tinnitus, which is not a single entity anyway. I now like to consider para-auditory somatosounds along with “idiopathic” tinnitus.

My current tinnitus model

I think of three steps in the creation of intrusive tinnitus and see them as the three main opportunities for therapeutic intervention — generation, perception and reaction.

Generation of tinnitus

Some assume that once an awareness of tinnitus has been triggered other mechanisms are entirely responsible for its continuation. However to overlook some ongoing generation of the activity which initially triggered the perception of tinnitus carries a risk of overlooking sites for useful intervention. Mechanisms, which cause tinnitus to become self-perpetuating, can themselves be regarded as

additional generators. Several sites for tinnitus generation are shown in bold type in Fig. 1. They offer a variety of possibilities for therapeutic intervention.

Within the inner ear decoupling of the microcilia of outer hair cells will have quite a different effect from detuning of the basilar membrane due to a reduction in the number of outer hair cells, which in turn is completely different from the effect of a general reduction in inner hair cells. Any resultant variation in activity in the auditory pathway may become interpreted as tinnitus. A total loss of inner hair cells in one part of the inner ear with preservation of normal inner ear hair cells adjacent to them produces a completely different “edge effect” in which the areas of the auditory cortex, which would normally respond to messages from the absent inner hair cells, acquire inappropriate stimulation that may be interpreted as noise. These and other pathologies within the cochlea may have different effects, which may lend themselves to different interventions. Damage to the fibers of the first order neurons might allow abnormal phase locking which might occasionally be a generator for tinnitus.

Para-auditory somatosounds may be eliminated or modified by direct attention to their generation even though the intrusiveness may result from central processing.

Attention to the non-auditory structures, which cause or aggravate somatosensory tinnitus can reduce or even eliminate awareness of the tinnitus.

Tinnitus may be triggered in the absence of any apparent peripheral contribution and persist after the auditory nerve has been divided. Neuroscientists demonstrate abnormal activity within the various parts of the brain in patients with tinnitus. Some new techniques enable clinicians to attack these central generators directly and a variety of therapies enable clinicians to modify them.

Psychological mechanisms

Clinicians have always recognized the importance of the emotional or affective reaction of a patient to their tinnitus and the factors, which were associated with its initial onset. Andersson and others

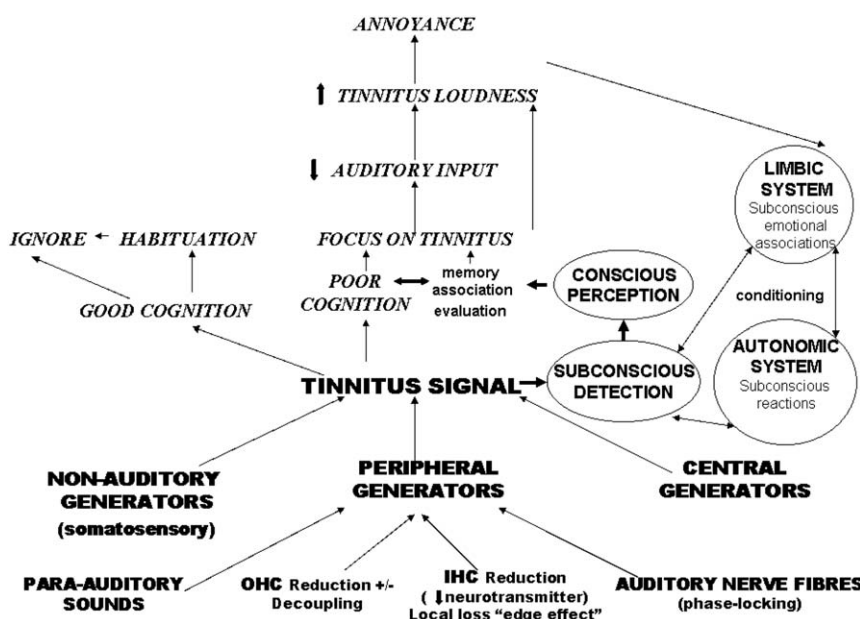


Fig. 1. A tinnitus model for explaining and planning management. Tinnitus generators are in bold type. Cognitive behavioral mechanism is in italics. Neurophysiological mechanism is within the balloons. Abbreviations: IHC = inner hair cells; OHC = outer hair cells.

(Andersson, 2003) have expanded and explained psychological mechanisms through the cognitive-affective model. However, I have found explanatory diagrams confusing. Figure 1 includes my simplified version of the consequences of poor cognition. With good understanding and lack of anxiety a potential tinnitus signal may be a “non-event”. However if understanding is poor and anxiety high the patient focuses on the tinnitus instead of normal auditory input and intrusiveness increases even at the expense of subjective hearing. Intrusiveness is further aggravated by associated emotional factors. As clinicians we want to improve our patient’s understanding of tinnitus, eliminate their anxiety about it, disassociate any emotional factors and refocus the patient’s attention on auditory activity resulting from external sound.

Neurophysiological mechanisms

Perhaps the most innovative tinnitus research ever achieved was that of Jastreboff and his colleagues in first conditioning guinea pigs to have tinnitus (Jastreboff and Sasaki, 1994). Having proved that

guinea pigs could be conditioned to have tinnitus it was appropriate to deduce that conditioning contributed to the development and perpetuation of intrusive tinnitus in humans. This approach diverts our attention away from the initial generation to conditioning within the reticular system influenced by unconscious emotional associations and autonomic responses as well as conscious emotional associations and reactions. My interpretation of the neurophysiological model is shown in balloons in Fig. 1. It is explained very clearly by Jastreboff himself elsewhere in this book. It followed that if conditioning could cause intrusive tinnitus then sound could be used to decondition patients from awareness of tinnitus. However deconditioning programs are most effective if generators are controlled, direct counseling has improved the patient’s understanding and if associated emotional factors have been disassociated. “Tinnitus retraining therapy” is well established and well proven, but relatively expensive of time and resource. I tend to expand on the neurophysiological mechanisms only with those patients for whom tinnitus retraining therapy or other deconditioning is going to be proposed.

Integrated model

Interventions available at specialized clinics may be based mostly on one or other of these models or of their components. However the general clinician dealing with a large number of patients needs to use a model which embraces all relevant factors and mechanisms so that we can identify the most appropriate components to focus on in developing a management plan or in deciding what type of specialized clinic our patient may need to be referred to. The model in Fig. 1 is the one on which I base my management of patients with tinnitus. I regularly modify it as my understanding and management evolve. Having the different components in differing colors makes it clearer for patients to understand. Differently constructed models will suit different clinicians and clinics specializing in particular types of treatment.

Assessment at the initial consultation

History (without questionnaires)

Following our research project of 30 years ago I initially incorporated all the same questionnaires into my regular clinical practice. A nurse practitioner helped each patient complete the questionnaires before I saw them. However my tinnitus patients then wanted to talk about and explore aspects of their tinnitus raised by the questionnaires and which had never occurred to them before. I therefore discontinued the practice. My tinnitus patients were then like all my other patients. They were able and wanted to tell me about the aspects of tinnitus, which had concerned them when they made the appointment in the first place. I felt that I was able to obtain from the patient a more accurate and appropriate history about the onset, character, fluctuations and progression of their tinnitus and about associated problems. I still use a checklist to ensure nothing is overlooked. For a while I tried to complete the questionnaires at the end of the consultation. However if the consultation had been successful and the patient was relieved and excited by what they had learned it became inappropriate to have them complete a questionnaire, which

raised issues, which were not previously relevant. Questionnaires play an important role in categorizing the tinnitus of those patients for whom tinnitus remains intrusive or even overwhelming. However for many of my patients presenting for the first time filling in questionnaires may magnify the problem and make it harder to treat.

Audiometry

An audiometric battery of tests is booked to immediately precede the consultation with me. Our basic battery for a patient with tinnitus and for most other otological problems includes pure tone air conduction and bone conduction, speech testing and tympanometry with reflexes. The audiologist checks that the ears are not occluded with wax. If they are then I clean the ears without starting the main consultation and send the patient back to complete their audiometry.

Examination

Almost all patients I see have been referred by their family doctor and the referral includes a computer printout of their general medical health, blood test results and medication. Occasionally while taking the history I may identify additional issues. Mostly I can confine my examination to my specialist areas.

I examine the nose, throat and, under the microscope, each ear. I am fastidious in removing all traces of wax, hairs and desquamated epidermis from the ear canals and off the drum surfaces. In this context I avoid suction so as not to induce any residual inhibition. Instead I use forceps and small balls of cotton wool smeared with ointment.

Temporomandibular joints are checked for crepitus and tenderness and the muscles of mastication and those of the neck for spasm and tenderness. I check for any influence on the tinnitus from grinding the molar teeth from side-to-side and from clenching the molar and then the incisor teeth together. I check for any change in the tinnitus from traction and compression on the head and from forcing the head to either side against my hand.

I then test for residual inhibition. I use noise from my suction apparatus and start with the worse

ear. I warn the patient to tell me immediately if they find the noise distressing so that I can instantly stop the test. It is quite rare that I need to do so. I hold an 18G suction tip in the center of the ear canal at the bony cartilaginous junction for 60 seconds. Immediately following the exposure I ask the patient whether their tinnitus in that ear is worse, unchanged or improved and if so whether it is greatly, moderately or just slightly improved. I also ask if the tinnitus in the other ear is more or less noticeable. Without waiting for recovery from residual inhibition I go ahead and test the other ear. If residual inhibition in the first ear was considerable then the patient may get a period of complete relief from tinnitus in both ears. Good residual inhibition is reassuring to the patient and also to me. Such patients tend to respond well to sound therapy.

I used to give many patients a test dose of intravenous lidocaine at their first appointment. However a high level of temporary relief from their tinnitus produced an expectation for a quick and complete cure, which could never be met. This made subsequent management more difficult. I now limit the lidocaine test to a small number of highly selected patients in whom the tinnitus has been very resistant to other treatments.

Treatments at the initial consultation

There are many treatment options available to help the clinician in managing a patient's tinnitus (Table 1). Only some are appropriate for use through a general clinic and at a first consultation. Some are sophisticated, time-consuming and expensive and are reserved for those patients who have not responded well to an initial treatment plan. They are delivered through a specialist tinnitus clinic following a secondary referral.

Correction of causes

Wax and otitis externa

I quite commonly find that troublesome tinnitus has subsided partly or completely following thorough cleansing of the ear canals and drum surfaces. Relief from tinnitus may occur even when

the audiogram and impedance tympanogram had been unaffected. In the past I have attributed this to relief from reflex spasm of tensor tympani. It may now be more appropriate to consider it a contributing factor in somatosensory tinnitus.

Conductive deafness

If there is a perforation I temporarily repair it with one or more rice paper patches moistened with aqueous ear drops. If tinnitus is relieved that constitutes a strong indication and motivation to arrange surgical repair.

If there is a negative middle ear pressure I attempt to temporally correct it by politizerization. Air is forced through the nose while the patient swallows to open their Eustachian tubes. I may then insert a mini grommet under topical anesthesia in my office. Relief from tinnitus focuses further management on the nose, Eustachian tube and middle ear.

Where conductive deafness is associated with stapedia fixation or other ossicular problems the tinnitus may respond to simple amplification. Any decision on surgical correction must be based on the benefits of potential hearing gain and on the associated risks and never only on the potential for relief from tinnitus.

Para-auditory somatosounds ("objective tinnitus")

These are most commonly suspected from the history and the source should be identified. Appropriate consultations are sought for the management of cardiac murmurs, vascular bruits and glomus tumors. Fasciculation of tensor tympani or tensor palati may correlate with problems of the jaw and neck. Where pulsatile tinnitus or other para-auditory noise does not justify intervention, its intrusiveness may be contributed to by many of the same factors, which cause subjective tinnitus to be intrusive and may respond to many of the same managements.

Reduction of aggravating factors

Factors which can be included under this category include stress, loud noise, caffeine, tinnitus inducing drugs, food and drink intolerances, neck strain,

temporomandibular disorder, metabolic abnormalities and dietary shortages. We have to be sensitive to the possibility of other factors which may be identified by the patient and suggest strategies to cope with them.

Stress

Stress plays a major role in inducing and maintaining tinnitus in some patients. However stress will aggravate the tinnitus of almost every patient. Therefore in almost every patient I discuss stress within the context of their usual lifestyle. I may suggest to them that in the natural environment stress is about fighting or escaping and that they need to balance their emotional stress with periods of vigorous physical activity.

Loudness intolerance

Tinnitus is often more noticeable in silence. However it may be aggravated by loud noise and remain more intrusive long after exposure to the loud noise has ceased. Where this is the case I suggest strategies to minimize exposure to loud noise. I may arrange appropriate active or passive hearing protection if exposure to loud noise is unavoidable.

Caffeine

Excessive caffeine consumption aggravates tinnitus and may cause it. Patients who drink many cups of coffee a day may cease to be aware of any tinnitus if they stop or greatly reduce their caffeine intake. They may need help to cope with troublesome withdrawal symptoms. It does not follow that everyone who has tinnitus should avoid caffeine completely. I sometimes suggest a 2-week trial without any caffeine and then resumption of the previous intake, which lets the patient discover very quickly if caffeine aggravates their tinnitus. If it does then the patient is motivated to minimize caffeine intake.

Tinnitus inducing drugs

The patient or their family doctor must always provide the clinician with a list of all the drugs they

are taking and the doses. I can then identify any of them, which may be causing or aggravating tinnitus and liaise with their family doctor to arrange a trial without the suspect drug.

Intolerances

A variety of foods and drinks (and tobacco) aggravate tinnitus in some patients but not others. The patient may be suspicious of some already. I provide the same advice as for caffeine in terms of temporary withdrawal and subsequent challenge. A negative challenge protects the patient from unnecessarily restricting their lifestyle.

Neck problems

Neck strain, whiplash and degenerative changes in the cervical spine predispose to, aggravate and possibly cause tinnitus. In some patients a few days trial in a soft collar may confirm the relationship but it is not appropriate long-term management. I ensure that such patients are getting good ergonomic advice especially for sitting at computers.

I have had a considerable number of patients whose tinnitus had been triggered or greatly aggravated by forceful manipulation of the neck. I do not hesitate to refer the patient to a physical medicine specialist. I know that neck manipulation helps some but I never have the confidence to recommend it.

Referral for training in abdominal respiration helps some of these patients possibly by relieving strain on the accessory muscles of respiration. I encourage patients with neck problems to swim crawl and breathe to alternate sides. It is cheap, effective and relaxing.

Temporomandibular disorder

This is a frequent aggravator of tinnitus. It is often associated with neck problems and disordered breathing and may respond to the same treatments. Patients are advised to avoid clenching and grinding of teeth and to use simple jaw and neck relaxing exercises from a pre-printed advice sheet, which I provide. They are asked to take a copy of my

report to their next dental appointment to ensure that their bite is adequately checked and if appropriate a bite plate fitted for them to wear at night.

Metabolic abnormalities and dietary shortages

Except where there are other problems such as a vestibular disorder I have had little success in finding unidentified metabolic abnormalities. This may be because nearly all my patients have been referred by their family doctor. I have failed to successfully identify dietary, vitamin and mineral deficiencies. I would welcome a suitable, authenticated list of agents to be tested for in the battery of blood tests arranged by the referring doctor.

Directive cognitive counseling

I would not pretend for one moment to be able to provide cognitive therapy. However providing a logical easily understood explanation of tinnitus is an essential part of managing every patient. *Reassurance without explanation is of little benefit no matter how prestigious the consultant.*

I find my patients do not relate well to diagrams, wall charts or large models. I use a life size model of the ear. I show the patient how we hear. I explain that sometimes when there is reduced hearing getting through the inner ear some of the hearing pathways may create extra information of their own which is perceived by the hearing centers as tinnitus. I may explain that sometimes hearing centers, deprived of adequate stimulation, become aware of other nerve activity within the brain which they then perceive as tinnitus. I may explain that messages from muscles of the neck and jaw interact within the brainstem on those from the balance and hearing parts of the inner ear and so may aggravate balance problems and tinnitus. The emphasis in my explanation is varied according to those mechanisms and managements which I think are most appropriate for each patient.

“The tinnitus does not matter. What matters is that you wish you were not aware of it. What can we do now that you understand?”

We then go back over possible causative and aggravating factors and identify the opportunities

for controlling them. Initially all the counseling is directive. Only once I am satisfied that the patient has grasped my explanations do I give them the opportunity to ask questions which I then answer on the basis of my preceding explanation (reactive counseling).

Disassociation of emotional factors

During the consultation it usually becomes clear the extent to which anger, fear, stress or depression may have played a major role in initiating intrusive tinnitus as well as perpetuating it. Fear and stress are easy to identify and talk about and usually respond well to explanation and general measures.

If there is a relatively mild degree of depression I frequently prescribe a small dose of tricyclic, usually nortriptyline starting with 10 mg at night and increasing to 10 mg in the evening and 20 mg at night. Used in addition to all the other measures I find that these small doses reduce anxiety and mild depression and may have a slight anticonvulsant action and reduce the tinnitus itself.

When there is more severe depression I seek help from a psychiatrist. However psychiatric help takes time to arrange. I continue with general measures for treating the tinnitus, I start the small dose of tricyclic and I ring the family doctor.

Anger associated with the onset and subsequent persistence of tinnitus makes that tinnitus very hard to treat. The tinnitus almost becomes an excuse for the continued anger and the patient may be quite uncooperative with any counseling or other management strategies. These patients need all the help we can arrange for them often from agencies we seldom otherwise deal with.

Sound enrichment: reduction of tinnitus to noise ratio

Where possible sound input is improved by correction of conductive problems. The patient is advised to avoid silence. I may have to persuade them that nobody likes silence. What they like are peaceful sounds. I encourage the patient to obtain recordings of relaxing environmental sounds such as rain, waterfall, sea or forest or of orchestral or

instrumental music. We discuss types of music, which may be appropriate. It needs to be of moderate tempo and major mode. The patient is told that talk back radio will only distract them and that talking and singing are of limited help because their influence is confined mostly to the language centers. I may encourage the patient to avoid silence even through the night by playing recordings continuously, using a pillow speaker if necessary. Some may elect to leave a fan or dehumidifier running in the bedroom because their spouse finds recordings unacceptable. A good response to the residual inhibition test acts as a strong motivator.

Hearing aids

If the patient was already aware of hearing difficulties and especially if there was good residual inhibition then I am keen to refer them for hearing aid fitting following the first consultation (see Chapter 32). On the other hand if they were barely aware of any hearing impairment and there was little or no residual inhibition then I think the question of hearing aids and/or noise generators is better deferred until other strategies have been utilized.

Written report

The patient is told that after the consultation I shall prepare a written report covering all aspects of the consultation and their tinnitus and that I shall send a copy to them as well as to their family doctor. Therefore they are not to worry if they cannot remember every detail of the consultation because the written report will cover it. I have always done this. *I regard a written report as an essential component of management.*

Follow-up

If I have put the patient on medication or some other treatment which needs follow-up then of course a follow-up appointment is made. However the majority of patients are told that I shall not make a follow-up appointment because I do not

expect them to need one. I tell them that if they have properly understood the explanations and adopt the strategies which we have discussed then I expect their tinnitus will gradually subside and that the less they think about it the sooner this is likely to occur. They are told that the last thing they need is an appointment to remind them about their tinnitus if their tinnitus has already become insignificant. However they are assured that they can ring my office at any time for further help. They are told that if needed there are specialist audiologists available to provide more sophisticated interventions both at our clinic and at the university clinic with which we have very strong links.

Repeat referral

For the majority of patients no further consultations are requested and for most of these it is because the tinnitus has ceased to be an important issue in their lives. We know this because of feedback from family doctors and because they have not sought appointments from my colleagues or from the audiological tinnitus clinics.

However some patients are very quick to seek an additional appointment. Mostly I have anticipated which these will be and my initial report has been structured accordingly. Other patients may be re-referred after months or years. When the patient rings for an appointment they are asked if they have re-read my original report. If they have forgotten about the report or mislaid it then we send them another copy and ask that they ring back for an appointment once they have read it. *More than half ring back to say that having re-read the report they have realized why their tinnitus is again an issue, that they are dealing with it and that they do not need another appointment after all.*

Some, especially those who have been seen very recently, I divert directly to the university or other audiological tinnitus clinic. The rest are seen again in my clinic. I reassess everything to ensure nothing has been overlooked or under estimated. If I do not identify ways in which my previous management can be improved on then most of these patients are referred on to the university or other audiological tinnitus clinics. An occasional patient

is so distressed that I may introduce medication, seek help from a psychiatrist, physical medicine or other specialist before referring them to an audiological tinnitus clinic.

Referral to an audiological tinnitus clinic

My relationship with these clinics is such that I know they will provide patients with the range of assessments and interventions, which I have neither the time nor the expertise to provide. This is a selected group of patients for whom tinnitus remains intrusive and intolerable, and therefore for whom focusing on their tinnitus through questionnaires and analysis will have no negative implications and for whom using a large amount of resource is fully justified.

At these clinics a full assessment will be repeated with extensive questionnaires, additional audiological testing and tinnitus loudness and annoyance measures.

Management will include further cognitive counseling, additional advice on sound enrichment, reconsideration and/or re-assessment of hearing aids, and may involve use of wearable noise generators, a formal program of tinnitus retraining therapy or tinnitus desensitization with music which has been spectrally modified according to the patient hearing loss (such as Neuromonics). Tinnitus coping strategies will be identified and recommended when appropriate.

Subsequent “on referral”

Other issues may be identified which are having a major influence on the tinnitus and interfering with its management. We have access to agencies skilled in person centered counseling. Social issues, family and financial problems may have to be addressed. Occasionally referral is made to those specializing in stress management, relaxation techniques; sleep disorders, breathing disorders, hypnotherapy and biofeedback. For some patients a holistic approach to diet, exercise, yoga and/or meditation can be helpful when other management has been disappointing.

Support groups

These can be of immense help for those in whom tinnitus remains extremely intrusive despite a wide range of interventions. Within a support group tinnitus sufferers do not feel isolated but rather enjoy the collegiality of meeting with others who share the same problem. Being part of a tinnitus support group can be a very positive experience. However because it is a selected group of tinnitus sufferers there is sometimes a tendency to share negative experiences or promulgate extremes of behavioral change or dietary restriction. As professionals we have to support both the support groups and our individual patients. One problem for support groups is that the more successful they are the more difficult it is for them to retain members. There may be a feeling that a person who has obtained benefit from membership has a responsibility toward the organization. On the other hand ceasing to think about their tinnitus was the therapeutic goal.

Desperate tinnitus patients

There are a small proportion of patients for whom tinnitus remains intolerable and so dominates their lives that they are not amenable to help from sound therapy in its various forms, from behavioral changes or from other measures, which require patient involvement. When confronted with this distressing situation the first step is always to review the influences of aggravating factors, the potential for correction of deafness and the thoroughness of previous explanation and understanding and sound therapy. When all these have failed then medication is our best chance to improve the tinnitus to a point at which these other measures may become effective.

I commonly introduce small doses of a tricyclic at quite an early stage in management and these patients may already be on nortriptyline 10 mg in the evening and 20 mg at night. In an urgent situation benzodiazepines are more rapidly effective and especially so when muscles of the neck and jaw are involved. Clonazepam has proved the easiest to use in my hands. Furthermore I find it easier to

subsequently wean the patient off clonazepam again compared with some other benzodiazepines such as alprazolam. I use .5mg tablets of clonazepam and start with one in the morning and two at night, then rapidly build up to twice that dose. I aim to wean the patient off it again over a total period of 2–3 weeks. During that time I ensure they are stabilized on a small dose of nortriptyline and that we have reintroduced sound therapy and any other applicable measures.

There are some cases when the patient is desperate and I am too. These are given a test dose of 2mg/kg of lidocaine intravenously over 10 minutes. The effect on their tinnitus is monitored. If there is a good response then I feel justified in introducing anticonvulsants. In most cases the patient ends up being on a cocktail of carbamazepine 100 mg twice through the day and 200 mg at night plus sodium valproate 200 mg twice through the day and 400 mg at night (in addition to continuing the small dose of nortriptyline). The dose of either or both the carbamazepine and sodium valproate may be increased considerably if side-effects are not excessive and regular monitoring of hematology and liver function is reassuring. These anticonvulsant drugs are best tolerated if introduced very slowly. If the situation is urgent and full doses are required immediately then I find treatment is best started in hospital. I stress that this is desperate treatment for desperate patients and is seldom needed especially nowadays when we have excellent support available from audiological tinnitus clinics.

The future

As a front line otologist I am relieved and delighted that we now have available to us specialist audiological clinics and a host of other specialties to which we can turn. However tinnitus is a very common complaint and I think that clinicians will always have to provide a management plan which meets expeditiously and effectively the needs of the majority of patients with tinnitus so that the minority for whom tinnitus remains severely intrusive can benefit from the intensive resources they require. I am pleased to see increasing attempts

to categorize patients with tinnitus so that we can identify the most appropriate management for each patient and each group of patients.

As research clinicians establish the therapeutic indications for new treatments such as transcranial magnetic stimulation so these treatments can be added to the list of options at other clinics. The chapters in this book fill me with hope because they demonstrate international co-operation, which will greatly facilitate further progress.

However in my experience if the ear canals and middle ears are healthy then there are only two mechanisms by which we can sometimes induce complete (though temporary) relief from tinnitus. These are residual inhibition after white noise and relief after intravenous lidocaine. Ultimately it may be the restoration of a normal hair cell population within the inner ear, which re-establishes a normal pattern of neural activity in the auditory pathways and centers. On the other hand it may be the techniques of the pharmaceutical biotechnology industry, which replicates the temporary effectiveness of intravenous lidocaine in a therapeutically effective form. Both are a long way off. The techniques we are using and investigating now are going to be relevant for a long time to come.

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CHAPTER 23

Drug treatments for tinnitus

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Abstract: Many of the drug treatments that are presently in use for tinnitus are aimed at either the cochlea, e.g. using intratympanic injections of gentamicin, dexamethasone or lidocaine, or the CNS using systemic delivery. Earlier benzodiazepines and anticonvulsants have been used and more recently, antidepressants have been introduced, partly in an attempt to treat the emotional aspect of tinnitus. The fact that there are many different forms of tinnitus with different and often multiple causes and that the pathophysiology is poorly understood, are obstacles to finding effective treatments. This situation has been exacerbated by the lack of clinical trials to formally test even some of the most commonly used drugs, as well as a lack of preclinical studies to investigate novel agents. It is suggested that the animal models of tinnitus that have been developed could be used to screen potential anti-tinnitus drugs as a preliminary step before conducting clinical trials.

Keywords: tinnitus; drug treatments; gentamicin; steroids; anticonvulsants; benzodiazepines

Introduction

Despite major advances in the understanding of the neurophysiological basis of some forms of tinnitus, and the development of several realistic animal models of the disorder, progress in the development of drug treatments has remained slow (Eggermont and Roberts, 2004; Baguley, 2006). Compared to other neurological disorders, relatively few systematic clinical trials have been conducted even for many of the drugs that are currently used to treat tinnitus (e.g., carbamazepine, gabapentin). Experimental and clinical studies of new drugs are emerging (e.g., memantine), but again only slowly and in a piecemeal fashion (Simpson and Davies, 1999; Smith and

Darlington, 2005). Given the availability of sensitive animal models of tinnitus, hopefully new and existing drug treatments can be screened for efficacy and then investigated in formal clinical trials, even if the exact mechanism of their action is not yet understood. The diversity of cause and pathophysiology of tinnitus is perhaps the greatest obstacle in developing efficient tests for the efficacy of new drugs.

There are many risk factors for subjective tinnitus, of which the greatest is age followed by cardiovascular and cerebrovascular diseases, noise exposure and different drugs (Hoffmann and Reed, 2004). Different kinds of subjective tinnitus have different 'ignition' mechanisms (Eggermont and Roberts, 2004; Baguley, 2006). While cochlear hair cell dysfunction may trigger noise-induced tinnitus, salicylate may cause tinnitus through several mechanisms, including direct action on the CNS in addition to effects on the cochlea (e.g.,

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Guillon et al., 2003; Liu et al., 2003; Basta and Ernst, 2004b; Liu and Li, 2004; Huang et al., 2005; Liu et al., 2005; Wang et al., 2006). The evidence that salicylate-induced tinnitus is correlated with neuronal hyperactivity in the auditory nerve is contradictory and unconvincing (e.g., Muller et al., 2003; see Eggermont and Roberts, 2004 for a review); however, most other forms of tinnitus appear to be associated with either a decrease in auditory nerve activity or no change (see Eggermont and Roberts, 2004 for a review). Nonetheless, salicylate is an *N*-methyl-D-aspartate (NMDA) receptor agonist (Guillon et al., 2003) and there is evidence to support the hypothesis that tinnitus is associated with neuronal hyperactivity in the central auditory nervous system and therefore, tinnitus may represent a form of sensory epilepsy that might be treatable with anticonvulsant drugs (Møller, 1997; Møller, 2000, 2003). This evidence is complicated and inconsistent, however.

Acoustic trauma has been correlated with increased spontaneous activity in the dorsal cochlear nucleus (Zhang and Kaltenbach, 1998; Kaltenbach and Afman, 2000; Brozoski et al., 2002; Zacharek et al., 2002; Kaltenbach et al., 2004; Kaltenbach and Zhang, 2007; Kaltenbach, 2006; however, contradictory *in vivo* data have been presented by Chang et al., 2002 and *in vitro* data by Ma and Young, 2006), the inferior colliculus (Wang et al., 2002; Basta and Ernst, 2004a) and the primary auditory cortex (Eggermont and Kenmochi, 1998; Norena and Eggermont, 2003; Seki and Eggermont, 2003; Eggermont, 2006). Cisplatin has been shown to cause hyperactivity in the dorsal cochlear nucleus (Melamed et al., 2000; Kaltenbach et al., 2002; Rachel et al., 2002). Studies of the effects of salicylate in the dorsal cochlear nucleus have not been published (Eggermont and Roberts, 2004).

There is evidence that salicylate can both increase and decrease the spontaneous neuronal activity in the inferior colliculus (compare Jastreboff and Sasaki, 1986; Chen and Jastreboff, 1995; Ma and Young, 2006), as well as decrease activity in the auditory cortex (Yang et al., 2007). If these animal studies represent the rationale for using drugs that increase CNS inhibition (e.g., benzodiazepine and anticonvulsant drugs) or reduce

excitation (e.g., NMDA receptor antagonists) to treat tinnitus in humans, then they do not present a very convincing picture but support the hypothesis that different forms of tinnitus have different neural mechanisms that require specific treatments. This may be why published clinical trials of such drugs have yielded inconsistent and sometimes negative results.

Epidemiological studies in the UK and Sweden have arrived at a prevalence of 10.2 and 14.2%, respectively (Hoffmann and Reed, 2004) (see Chapter 1). Epidemiologic studies of tinnitus have a large degree of uncertainty, and depend on the definition of tinnitus. In the US tinnitus has been estimated to represent a potential market of US \$10 billion (Vio and Holme, 2005). Despite this, there is very little consensus on the best drug therapies for this condition. The aim of this review is to summarise and critically evaluate the most recent evidence relating to drug treatments for tinnitus and to suggest new avenues for expediting the investigation of novel drug treatments.

Intratympanic drug treatment

Intratympanic administration of gentamicin has been used successfully to treat Ménière's disease and therefore to treat tinnitus associated with Ménière's disease (see Smith, 2000 for a review). The rationale behind this therapy is that aminoglycoside antibiotics such as gentamicin are ototoxic and therefore can be used to reduce activity in the affected ear. Diamond et al. (2003) reviewed the clinical trial data and concluded that intratympanic gentamicin reduced tinnitus in approximately 57% of patients. Similar conclusions were reached by Dodson and Sismanis (2004). A 5-year follow-up study failed to find any significant benefit for hearing (Atlas and Parnes, 2003), Lange et al. (2004) have reported a significant reduction of tinnitus in 50% of patients treated with intratympanic administration of gentamicin for 2–4 years. They found that permanent gentamicin ototoxicity could be prevented if an interval of 7 days between injections was used. Suryanarayanan and Cook (2004) found that tinnitus was reduced in 68% of their patient sample. However, it is worth

noting that many patients with permanent gentamicin ototoxicity also experience tinnitus (Black et al., 2004), and therefore it is important that the interval between injections is sufficiently long to avoid ototoxicity (Lange et al., 2004). The effects of gentamicin on cochlear hair cells may be mediated in part by NMDA receptors (see Smith, 2000 for a review).

Intratympanic steroid treatment has also been used to treat tinnitus of peripheral origin. Schulman and Goldstein (2000) reported that 7 out of 10 patients studied experienced relief from tinnitus following intratympanic steroid treatment, although tympanic membrane perforation lasted for more than 6 months in 2 patients. In a larger study, Cesarani et al. (2002) found that of 50 patients treated with intratympanic dexamethasone, in 34% tinnitus disappeared and in 40% it decreased in intensity. Garduno-Anaya et al. (2005) studied 22 patients with unilateral Ménière's disease and found that intratympanic dexamethasone relieved tinnitus in 48% of the patients. This was a prospective, randomised, double-blind, placebo-controlled trial and therefore probably presents the most convincing evidence to date, since many other studies have been retrospective and uncontrolled (Dodson and Sismanis, 2004; Doyle et al., 2004). Nonetheless, Araujo et al. (2005), also using a prospective, randomised, placebo-controlled but single-blind trial, reported that intratympanic dexamethasone had no significant effect on severe tinnitus compared to placebo. Methylprednisolone has also been used to treat sudden hearing loss in one open label trial, but the effects on tinnitus were negligible (Slattery et al., 2005a). From a retrospective review, Haynes et al. (2007) concluded that intratympanic dexamethasone had positive effects in patients with sensorineural hearing loss, in whom tinnitus was one associated symptom.

Sakata et al. (2001) investigated the effects of intratympanic administration of 4% lidocaine on tinnitus and found that it had a positive effect in 81% of a sample of 292 patients. Unfortunately, vestibular symptoms, including vertigo, often developed following the infusion. The muscarinic acetylcholine receptor agonist, carbachol, and the acetylcholinesterase inhibitor, pilocarpine, have

also been used intratympanically; however, while they relieved tinnitus in 50% of patients, the benefit was short-lived and tinnitus returned with its original intensity after 12–72 h (DeLucchi, 2000).

Intravenous lidocaine

The use of local anaesthetics for the treatment of tinnitus dates back to 1937 (Simpson and Davies, 1999). Many studies have shown that i.v. lidocaine can alleviate tinnitus, although the mechanism of action is unknown. It was shown early that lidocaine could alleviate tinnitus temporarily in Ménière's disease (Gejrot, 1963). More recently, Otsuka et al. (2003) examined its effects over a 2 4-year period in 103 patients, and concluded that it relieved tinnitus partially or completely in approximately 71% of cases. Marzo et al. (2004) found that it relieved tinnitus caused by inner ear tertiary syphilis. Unfortunately, few of the data supporting the use of lidocaine comes from large, well-controlled clinical trials with placebo controls and double-blind methodology. Kalcioğlu et al. (2005) reported subjective relief from tinnitus that lasted up to 4 weeks and there were no significant differences in either spontaneous or distortion product otoacoustic emissions. Lidocaine administered i.v. thus does not seem to affect otoacoustic emissions indicating that its effect on tinnitus is not on the cochlea. It is still unclear how lidocaine might work to alleviate tinnitus (Trellakis et al., 2006), although it is possible that since it may work intratympanically it might produce either vasodilatation or sodium channel blockade in the cochlea (Sakata et al., 2001, see also Chapter 28).

Studies in patients in whom the auditory nerve had been severed during removal of a vestibular schwannoma show that i.v. lidocaine can suppress tinnitus (Baguley et al., 2005), indicating that the effect of lidocaine on that form of tinnitus must be on the central nervous system (Manabe et al., 1997). There are, however, also indications that some of the positive effects of lidocaine in uncontrolled trials may be due to expectation, i.e., the placebo effect.

Savastano (2004), used intradermal lidocaine in 68 patients and found that it relieved tinnitus. The

lidocaine analogue, mexiletine, has also been used with some success for treatment of tinnitus (Berninger et al., 2006). An earlier lidocaine analogue, tocainide, was used but is no longer available in some countries, e.g., USA (Larsson et al., 1984).

Osmotic regulators and vasodilators

Ménière's disease is defined as a triad of symptoms: tinnitus, fluctuating hearing loss and vertigo. Since these symptoms are associated with hypertension of the labyrinthine endolymphatic fluid, diuretics have been used to treat the symptoms of Ménière's disease, including tinnitus. The loop diuretic, furosemide, has been used with some success (Simpson and Davies, 1999). However, in a review of the literature between 1966 and 2005, Thirwall and Kundu (2006) concluded that there was insufficient evidence that diuretics have any significant effect on tinnitus or the other symptoms of Ménière's disease. Use of other drugs that regulate osmotic pressure, such as glycerol and mannitol, have had limited success in alleviating tinnitus in Ménière's disease (Simpson and Davies, 1999).

Although vasodilators were once thought to be effective in individuals with Ménière's disease, recent studies have not confirmed their efficacy in alleviating tinnitus (Simpson and Davies, 1999). However, misoprostol, a synthetic prostaglandin E1 analogue that stimulates vasodilatation, has been shown to be effective in about one third of tinnitus patients (Simpson and Davies, 1999). Yilmaz et al. (2004), using a double-blind, placebo-controlled design, found that misoprostol reduced the loudness of tinnitus in 18 out of 28 patients studied (see also Akkuzu et al., 2004).

Benzodiazepines

Benzodiazepines are GABA_A receptor agonists and may therefore be expected to reduce the hyperactivity that may cause tinnitus (Goldstein and Shulman, 2003). Gananca et al. (2002), in a retrospective survey of 25 years of the use of clonazepam in the treatment of tinnitus, concluded

that it was at least partially effective in 32% of cases. Shulman et al. (2002) has suggested that benzodiazepines can provide long-term relief in 90% of patients with tinnitus of central origin. Unfortunately, there are no systematic well-controlled clinical trials (i.e., double-blind, placebo-controlled) of the effects of benzodiazepines on tinnitus. Even if they were effective it is conceivable that they could work either by having a general anxiolytic effect (Simpson and Davies, 1999) or by reducing neuronal activity by a mechanism not involved in the generation of tinnitus.

Suneja et al. (1998) reported a decrease in the release and the reuptake of GABA in the dorsal cochlear nucleus up to 145 days after unilateral cochlear lesions in guinea pigs. A decrease in GABA release has also been found in the inferior colliculus following bilateral cochlear lesions (e.g., Bledsoe et al., 1995). Signs of hyperactivity in the inferior colliculus from noise exposure can be reversed by administration of benzodiazepines (Szczepaniak and Möller, 1995). Receptor binding studies in animal models of tinnitus suggest a decrease in the number of GABA_A receptor binding sites in the inferior colliculus, with an increase in affinity (e.g., Bauer et al., 2000). However, no such studies have been published on the cochlear nucleus. With this in mind we have recently investigated the expression of the $\alpha 1$ GABA_A subunit in the cochlear nucleus in salicylate-induced tinnitus and found a decrease in the number of neurons expressing this protein in both the dorsal and ventral cochlear nucleus (Zheng, Sawant, Smith and Darlington, in prep.). Such changes are consistent with, but do not prove, the hypothesis that a decrease in GABAergic systems is responsible for hyperactivity in the central auditory system that may underlie tinnitus (Shulman et al., 2000; Daftary et al., 2004).

Even if benzodiazepines were effective in relieving tinnitus, one of the disadvantages of their use is adverse side effects such as sedation.

Non-benzodiazepine anticonvulsant drugs

Many other anticonvulsant drugs have been investigated for their efficacy against tinnitus,

although once again there is a shortage of well-controlled clinical studies. Most anticonvulsant drugs such as sodium valproate, phenytoin and carbamazepine work by inhibiting voltage-dependent sodium channels; therefore, if tinnitus was caused by neuronal hyperactivity, such drugs might be expected to provide some relief. Although many of these drugs have considerable adverse side effects when given in dosages used to treat epilepsy, they could possibly alleviate tinnitus when given in lower dosages. Menkes and Larson (1998) published a single case study reporting that sodium valproate was effective in suppressing tinnitus, but to the best of our knowledge, properly controlled clinical trials to evaluate its potential efficacy have not been published.

Carbamazepine has been used to treat tinnitus, but other than case studies (e.g., Menkes and Larson, 1998; Levine, 2006), only three trials have been published. Melding and Goodey (1979) reported that 56% of patients that had responded positively to lidocaine experienced relief from tinnitus following carbamazepine treatment. Sanchez et al. (1999) also reported that carbamazepine was effective in reducing tinnitus in 58% of patients

and abolished tinnitus in 18% of patients. However, Hulshof and Vermeij (1985) reported that carbamazepine was less effective than placebo in relieving tinnitus. We investigated the efficacy of carbamazepine against salicylate-induced tinnitus in rats and found that it protected against tinnitus-related behaviour in a dose-dependent fashion (Zheng et al., 2007, *in press*; see Fig. 1). This result, albeit in an animal model, suggests that carbamazepine may be worthy of further investigation for the treatment of tinnitus.

Gabapentin is by far the most studied anticonvulsant drug for the treatment of tinnitus (Goldstein and Shulman, 2003). Following a positive case study (Zapp, 2001), Bauer and Brozoski (2006) conducted a prospective, placebo-controlled, single-blind trial of the effects of gabapentin on 39 patients with tinnitus (see Chapter 27). They found that the drug was effective in reducing tinnitus in some patients, especially those in whom the condition was related to acoustic trauma. However, more recently, Witsell et al. (2007), using a randomised, placebo-controlled, double-blind trial, reported that gabapentin had no significant effect on the severity of tinnitus.

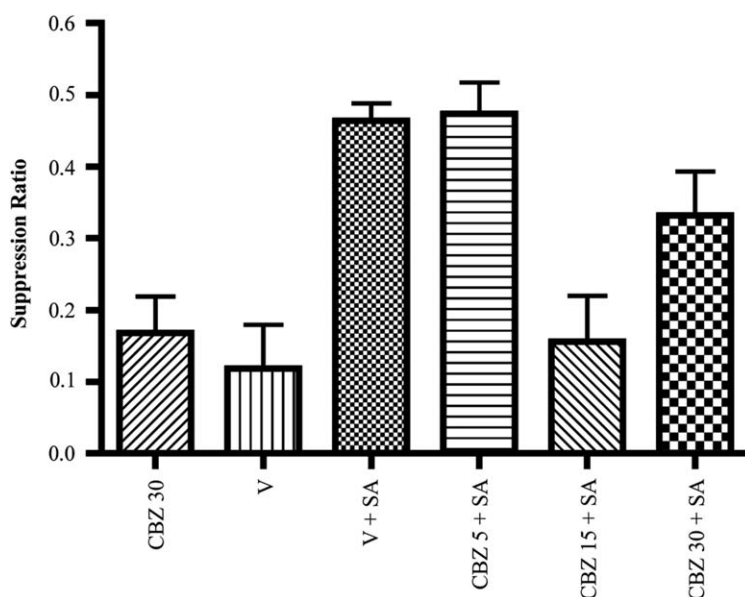


Fig. 1. Mean suppression ratios (SRs) on extinction day 1 for the groups ($n = 6$) receiving CBZ 30 mg/kg alone (CBZ 30), vehicle alone (V), vehicle + salicylate (V + SA), CBZ 5 mg/kg + SA (CBZ5 + SA), CBZ 15 mg/kg + SA (CBZ15 + SA) or CBZ 30 mg/kg + SA (CBZ30 + SA). Bars represent means \pm 1 SD. Adapted with permission from Zheng et al. (2007, *in press*).

Antispasticity drugs

Baclofen, a GABA_B receptor agonist, has been used to treat tinnitus, but with little success and substantial adverse side effects (Simpson and Davies, 1999). In a randomised, double-blind, placebo-controlled clinical trial, Westerberg et al. (1996) found that baclofen was no more effective than placebo in relieving tinnitus; however, some 26% of patients withdrew due to the adverse side effects of the drug.

Although there are very few data relating to GABA_B receptor expression in the brain during tinnitus, we have recently found that salicylate-induced tinnitus in rats is correlated with a down-regulation of the B1 GABA_B subunit in the dorsal and ventral cochlear nuclei (Zheng, Sawant, Smith and Darlington, in prep.). Animal experiments (rats) have shown that signs of hyperactivity in the inferior colliculus induced by noise exposure can be reduced by administration of L-baclofen while D-baclofen had no effect (Szczepaniak and Møller, 1995).

NMDA receptor antagonists

In addition to increasing inhibition in the CNS, another strategy for reducing neuronal activity associated with tinnitus, is to reduce excitation. Some animal studies have suggested that tinnitus is associated with an upregulation of glutamate receptors in the cochlear nucleus (Muly et al., 2004). We have also found an increase in the number of neurons expressing neuronal nitric oxide synthase (nNOS) in the ventral cochlear nucleus following salicylate treatment, and nNOS expression is often linked to NMDA receptor activity (Zheng et al., 2006; see Fig. 2). The non-selective glutamate receptor antagonist, caroverine, has been reported to relieve tinnitus in 63% of patients (Denk et al., 1998). In general, even selective NMDA receptor antagonists have been associated with severe adverse side effects such as psychotic symptoms (Kemp and McKernan, 2002; Smith, 2003). However, memantine and a group of NR2B-selective NMDA receptor antagonists have proven to be well tolerated by patients and have been used in the treatment of neuropathic pain (Parsons et al.,

1999; Kemp and McKernan, 2002; Smith, 2003). To the best of our knowledge, memantine has not yet been investigated in humans for treatment of tinnitus; however, Lobarinas et al. (2006), who recently studied its efficacy against salicylate- and quinine-induced tinnitus in rats, found that memantine failed to reduce tinnitus-related behaviour or cortical auditory evoked potentials to a statistically significant extent.

The effect of another NMDA receptor antagonist, flupirtine, on tinnitus has been investigated in humans, but, no significant effects were observed (Salembier et al., 2006). Topical application of caroverine to the tympanic membrane is also being investigated, with encouraging preliminary results (Ehrenberger, 2005).

Antidepressants

Many case reports of antidepressants being used to treat tinnitus have been published but the results of only a few systematic, well-controlled trials have been reported (see Robinson et al., 2007 for a review Chapter 24). Folmer and Shi (2004) found that patients who developed depression following the onset of tinnitus exhibited a significant decrease in tinnitus severity and depression when evaluated after 20 months of treatment with antidepressants (selective serotonin reuptake inhibitors, SSRIs). In a randomised, placebo-controlled, double-blind study, Zoger et al. (2006) found that sertraline significantly reduced tinnitus compared to placebo, with modest side effects. However, Robinson et al. (2005) found that paroxetine had no consistent effects on tinnitus in patients who were not depressed. Most recently, Robinson et al. (2007) have reviewed the literature on the use of antidepressants to treat tinnitus and concluded that further trials are needed to replicate the results of the few trials that have been published to date. Baldo et al. (2006) have concluded that there is insufficient evidence to conclude whether antidepressants are effective in treating tinnitus.

Anticholinergic drugs

There are indications from animal experiments of abnormalities in the function of cholinergic

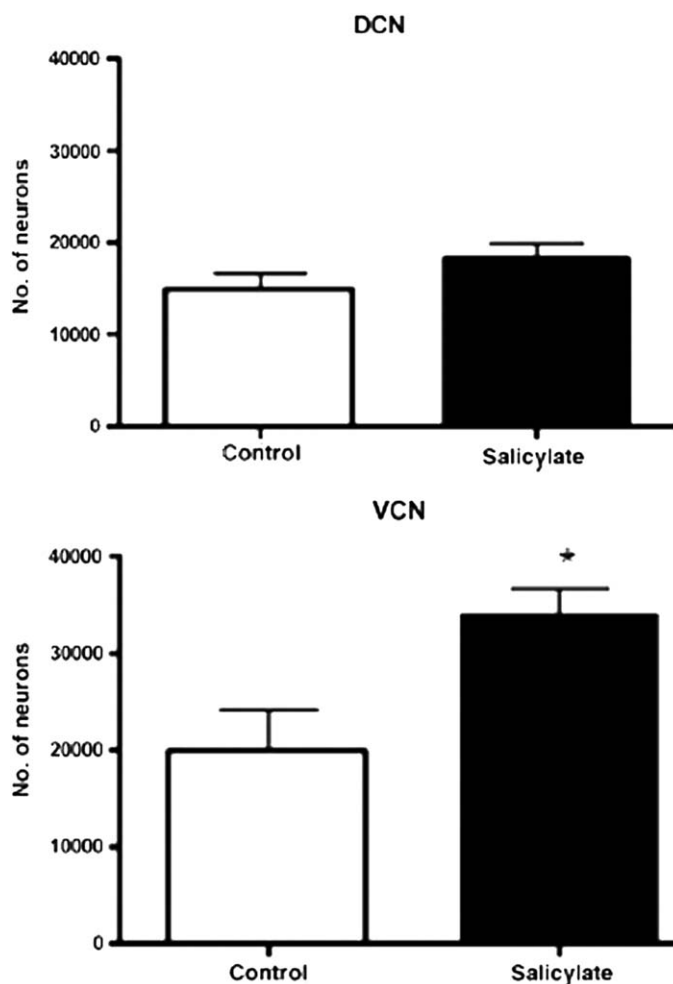


Fig. 2. Comparison of the number of neurons in the dorsal and ventral cochlear nuclei (DCN and VCN) expressing neuronal nitric oxide synthase (nNOS) following salicylate (Sa) or vehicle (control) treatment. Bars represent means \pm 1 SD. Adapted with permission from Zheng et al. (2006).

systems after exposure to loud noise that is likely to cause tinnitus. Thus Jin et al. (2006) reported that hamsters exposed to loud noise exhibited a large and sustained increase in choline acetyltransferase in the cochlear nucleus, suggesting an increase in acetylcholine production. Kaltenbach and Zhang (2007) have also reported an increased response to the acetylcholine receptor agonist, carbachol, in the dorsal cochlear nucleus of noise-exposed rats, possibly as a result of an upregulation of acetylcholine receptors (although changes in affinity or efficacy of the receptors could also account for the result). Wallhausser-Franke et al.

(2006) found that the muscarinic acetylcholine receptor antagonist, scopolamine, blocked plasticity in the auditory cortex that was associated with tinnitus, further suggesting that anticholinergic drugs may be useful in treating tinnitus. However, results of clinical trials of anticholinergic drugs have not yet been published.

Ginkgo biloba extracts

Much has been claimed regarding the efficacy of *Ginkgo biloba* extracts in the treatment of tinnitus.

Unfortunately, the reality is that there is no reliable evidence at all that they have any effect at the doses normally used in humans.

Hilton and Stuart (2004) reviewed the literature and concluded that there were insufficient reliable data from which to draw a conclusion; most of the available studies were flawed methodologically. Few studies have used double-blind, placebo-controlled designs, and the results of those that have used such techniques showed no significant effect of the extract compared to placebo (Drew and Davies, 2001; Meehan et al., 2004; Rejai et al., 2004; Smith et al., 2005). To date, only one study of the effects of EGb 761 on salicylate-induced tinnitus using a conditioned behaviour paradigm in rats has been published (Jastreboff et al., 1997). In this study, daily oral administration of 25, 50 and 100 mg/kg EGb 761 was found to reduce tinnitus behaviour compared to vehicle. However, it should be noted that these are very high doses and it is unlikely that they could be used in humans without adverse side effects (25 mg/kg/day for a 70 kg adult corresponds to 1750 mg/day, which is more than 7 times the average daily dose used in humans).

Other drug treatments

Many other drugs have been investigated for their effect on tinnitus. Novotny and Kostrica (2002) examined the efficacy of cinnarizine/dimenhydrinate and betahistine, drugs commonly used to treat vestibular disorders, against tinnitus associated with Ménière's disease and found that this drug combination reduced tinnitus in approximately 60% of patients. Mora et al. (2003), recognising the potential importance of thrombotic factors in the development of tinnitus, tried the anticoagulant, enoxaparin, which is a low molecular weight heparin, in 20 patients with tinnitus. All of the patients receiving enoxaparin experienced a reduction in their tinnitus, and no adverse side effects were noted.

There is some evidence that systemically administered steroids can alleviate tinnitus that occurs together with sensorineural hearing loss (Narozny et al., 2004; Slattery et al., 2005b). For example,

Slattery et al. (2005b) reported that such tinnitus was relieved following a 14-day course of prednisone. Recently, Lopez-Gonzalez et al. (2007) have investigated the effects of the D2 dopamine receptor antagonist, sulpiride, in combination with administration of the sedative, hydroxyzine, on tinnitus. They found that tinnitus perception was reduced in 56% of the patients treated with sulpiride alone and in 81% of the patients treated with the drug combination. This clinical trial was motivated by the novel hypothesis that dopamine pathways are involved in the pathology of tinnitus.

Other drug treatments that have been suggested to be useful in the management of tinnitus include acamprosate (Azevedo and Figueiredo, 2005) (see Chapter 25), melatonin (Megwalu et al., 2006) (see Chapter 30) and dronabinol. (Raby et al., 2006). With respect to cannabinoids such as dronabinol, which is a synthetic form of delta-9-tetrahydrocannabinol (THC), it is interesting to note that they may have anticonvulsant effects under some circumstances and therefore it is possible that they could modulate the severity of tinnitus (Smith and Darlington, 2005). At this stage, not much is known about cannabinoid receptors in the central auditory system; however, we have recently found that cannabinoid CB1 receptors are down-regulated in the ventral cochlear nucleus in salicylate-induced tinnitus in rats (Zheng et al., 2007; see Fig. 3).

Conclusions: problems and opportunities

At the present time, there is no clear consensus regarding the best drug treatments for tinnitus. While this may be partly due to a lack of well-controlled clinical trials and apparent discrepancies between the available trials, it is also likely to be due to the fact that tinnitus has many different causes and therefore, different drugs may be effective for different types of tinnitus. While intratympanic administration of gentamicin, steroids or lidocaine, as well as vasodilators and anticoagulants, may be useful in treatment of tinnitus that is associated with Ménière's disease and which may be of peripheral origin, these drug strategies may have limited utility in cases where tinnitus is

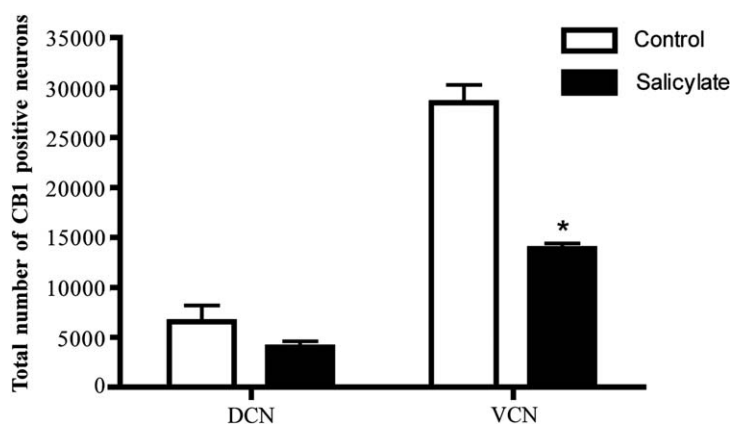


Fig. 3. Total number of CB1 positive neurons in the dorsal and ventral cochlear nuclei (DCN and VCN) in control (open bars) and salicylate treated (filled bars) rats. Data are expressed as mean \pm s.e.m. * $P < 0.01$ compared with the control group. Adapted with permission from Zheng et al. (2007, accepted pending minor revision).

caused by a central pathology (even if it was initially triggered by a peripheral event such as acoustic trauma). In the latter case, the drug treatment options become benzodiazepines, anti-convulsants, NMDA receptor antagonists or anti-depressants. None of these categories of drugs has received overwhelming support from published studies, and again, this is probably due in part to a lack of well-controlled studies as well as differences in centrally produced tinnitus. Mapping studies indicate that many different parts of the CNS, including limbic regions, undergo changes in connection with tinnitus (Lockwood et al., 1998) (see also Chapter 3). Which changes are part of the cause of the condition, and which may be an effect, is difficult to determine (Wallhauser-Franke et al., 2003; Mahlke and Wallhauser-Franke, 2004). The ‘distributed’ nature of the neural abnormalities underlying tinnitus suggests that many types of tinnitus could benefit from systemic drug therapy.

One of the major advances in the understanding of the neurobiology of tinnitus in the 1980s was the development by Jastreboff and colleagues of neurophysiologic models of tinnitus (Jastreboff, 1990), and the development of animal models using conditioned suppression paradigms (Jastreboff and Sasaki, 1986, 1994; Jastreboff et al., 1988; Brennan and Jastreboff, 1991; Jastreboff and Brennan, 1994) (see Chapter 40). These models, all of which involve associating the tinnitus

sensation with some form of conditioned stimulus, so that the animal changes its behaviour, have been modified and extended by others (Bauer et al., 1999; Bauer and Brozoski, 2001; Heffner and Harrington, 2002; Rüttiger et al., 2003; Brozoski and Bauer, 2005; Heffner and Koay, 2005; see Fig. 4 for an example) (see also Chapters 41, 42, 43 and 44).

It has been reported that an enriched auditory environment can reduce the extent of hearing loss following acoustic trauma (Norena and Eggermont, 2005) and one interesting possibility for future investigation is that the combination of specific types of drug therapy together with auditory stimulation might provide a treatment for tinnitus that is superior to either therapy alone. In this regard, it may be well worth investigating the efficacy of drug treatments with psychological therapy as well as the effects of combinations of drug treatments.

The animal models of tinnitus mentioned above have not been exploited as much as they might have been for the screening of potential anti-tinnitus drugs and few novel drug treatments have been investigated using these methods. This is a deficiency that requires urgent redress (Baguley, 2006). Using automated conditioned suppression paradigms, it should be possible to conduct pre-clinical evaluation of a large number of potentially useful drugs as a prelude to conducting formal

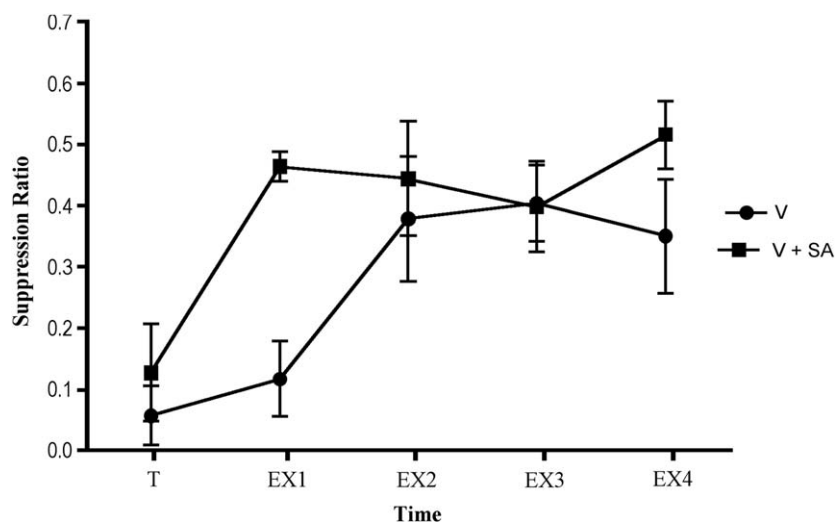


Fig. 4. Suppression ratios for training (T) and the 4 extinction days (EX1–EX4) for vehicle-treated (V) and salicylate-treated (V + SA) rats ($n = 6$ per group). Note the increase in the SR for the V + SA group on EX1 when the SA treatment was administered. Symbols represent means ± 1 SD. Adapted with permission from [Zheng et al. \(2007, in press\)](#).

clinical trials. There is also, of course, an urgent need for more clinical trials that employ the gold standard double-blind, placebo-controlled design ([Tyler et al., 2006](#)).

Acknowledgements

This research was supported by grants generously provided by the Jean Cathie Estate. We thank Katie Hooton for her assistance with the literature review.

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CHAPTER 24

Antidepressants for treatment of tinnitus

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Abstract: Antidepressants are commonly prescribed for tinnitus. Research thus far provides some support for that treatment, but the literature also raises concerns because tinnitus is a side effect of antidepressant medication. In this chapter, four published double blind placebo-controlled trials of antidepressants for tinnitus are reviewed. Explanations for the discrepant results are offered, including that antidepressants appear to work best for tinnitus patients who are depressed or anxious, who have more severe tinnitus or who are treated for a longer time with an adequate dose of medication. Possible mechanisms of action are reviewed, with serotonergic and antimuscarinic mechanisms appearing to be the most important. At this time there is no indication that one specific type of antidepressant is more likely to lead to tinnitus as a side effect, or have a beneficial effect on tinnitus. Given SSRIs are tolerated better, these antidepressants have advantages over tricyclic antidepressants and should be used as a first line of treatment.

Keywords: antidepressant; tinnitus; selective serotonin reuptake inhibitor; tricyclic antidepressant

Introduction

Antidepressants are the most commonly prescribed medication for tinnitus (Parnes, 1997). Most patients with tinnitus are treated by otolaryngologists and audiologists, and in the USA that means that most of the antidepressants for tinnitus are prescribed by otolaryngologists who may have limited knowledge about such drugs. The current generation of antidepressants is referred to as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Examples of SSRIs include Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline), Celexa (citalopram), Lexapro (escitalopram), Remeron (mirtazapine) and Desyrel (trazadone). Effexor (venlafaxine) and

Cymbalta (duloxetine) are two popular SNRIs. Wellbutrin, also known as Zyban (bupropion), is included in the current generation of antidepressants but it does not affect serotonin; instead it inhibits the uptake of norepinephrine and dopamine. The older generation of antidepressants includes tricyclic antidepressants and monoamine oxidase inhibitors. Tricyclic antidepressants include Elavil (amitriptyline), Sinequan (doxepin), Tofranil (imipramine), Norpramin (desipramine), Pamelor (nortriptyline) and Surmontil (trimipramine). Monoamine oxidase inhibitors, such as Nardil (phenelzine) and Parnate (tranylcypromine), are rarely used because of the potential drug–drug and drug–food interactions resulting in hypertensive crisis and serotonergic syndrome, but are still occasionally prescribed for the treatment of refractory depression. The commonality across all antidepressants is an effect on serotonin and norepinephrine.

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Antidepressants primarily differ in their side effects, with the tricyclic antidepressants having more anticholinergic and antihistaminic side effects than the current generation of antidepressants. SSRIs and SNRIs are the first choice for the treatment of depression and anxiety disorders due to better tolerability than tricyclic antidepressants, which are anyhow still frequently prescribed for pain and insomnia. Physicians prescribing SSRIs and SNRIs should be careful to avoid serotonergic withdrawal syndrome; usually consisting of muscle aches, headaches, nausea, fatigue, dizziness/light-headedness and irritability. The usual onset of withdrawal symptoms is approximately 36 h after the last dose of an antidepressant. Serotonin withdrawal is most likely to occur with paroxetine and venlafaxine, but may occur with any SSRI or SNRI, especially if the dose of drug used was high. To prevent serotonin withdrawal syndromes, SSRIs or SNRIs should be gradually decreased in dose instead of being abruptly discontinued.

Antidepressants that cause tinnitus

Tinnitus has been reported as a side effect of nine of the ten drugs included in the current generation of antidepressants, of all tricyclic antidepressants and of both monoamine oxidase inhibitors (for a review see (Robinson et al., 2006)). A retrospective chart review of 475 people on tricyclic antidepressants found 1% of those taking imipramine complained of tinnitus (Tandon et al., 1987). Feighner described tinnitus to be a side effect of imipramine in a double blind randomized parallel group study (Feighner et al., 1981), and of fluoxetine as part of a double blind parallel group trial for major depression (Feighner, 1985). In a double blind placebo-controlled study of paroxetine for treatment of tinnitus (see page 274), 2 of 61 (3%) patients discontinued the investigation due to a perceived worsening of tinnitus (Robinson et al., 2006). Onset of this adverse event has been reported to manifest as rapidly as 30 min after taking amitriptyline (Miles, 1980) or as long as 5 weeks after starting phenelzine (Glass, 1981). It often occurs after a dose has been increased (Racy and Ward-Racy, 1980; Golden et al., 1983).

Based on the above information, it does not appear that tricyclic antidepressants are more or less likely to cause tinnitus as a side effect than the current generation of antidepressants (SSRIs and SNRIs).

Despite the numerous reports of tinnitus as a side effect of antidepressants, it is difficult to establish the cause and effect. Most package inserts for antidepressant drugs where tinnitus is listed as a side effect do not provide the incidence compared to that of placebo. Additionally, trials aimed at gaining FDA approval for antidepressants were not designed to look at the incidence of side effects; and therefore it is unknown if the incidence of tinnitus in persons on antidepressant drugs is greater than that of the general population. In all of the reported studies where the participants were followed after having stopped the antidepressant, tinnitus resolved within 3 weeks. In some of the reports, the antidepressant drug was retried and the side effect recurred (Glass, 1981; Golden et al., 1983; Feder, 1990; Settle, 1991; Ahmad, 1995). Further complicating matters is the fact that the development of tinnitus varies widely from person to person, drug to drug and even dose to dose. Although one antidepressant may lead to tinnitus in a particular person, it does not mean that another antidepressant will have the same effect (Evans and Golden, 1981; Glass, 1981).

Certain strategies have been tried for reducing the tinnitus when it appears with the onset of administration of antidepressants. One strategy is to change the dose, for example from 150 mg per day to 50 mg three times a day (Miles, 1980). Another strategy that has been effective at resolving this condition in some cases is reduction in total daily dose of medication (Racy and Ward-Racy, 1980; Golden et al., 1983). Multiple patients have also simply stayed on the medication and found that the tinnitus resolved within 2 weeks to 9 months after onset (Tandon et al., 1987; Laird and Lydiard, 1989; Settle, 1991).

Two case reports of tinnitus occurring as part of withdrawal from venlafaxine and sertraline have also been published (Leiter et al., 1995; Farah and Lauer, 1996). In the venlafaxine case, the medication was restarted and the serotonin

withdrawal symptoms resolved, and in the sertraline case, all symptoms resolved within 14 days of discontinuing the medication.

Antidepressants that may benefit tinnitus

Despite that some antidepressants have tinnitus as a side effect, certain antidepressants are effective in treating some forms of chronic tinnitus in some individuals. Three of the four double blind placebo-controlled protocols for treatment of tinnitus with antidepressants that have been published, found the treatment beneficial — see Table 1 (Mihail et al., 1988; Sullivan et al., 1993; Robinson et al., 2005; Zoger et al., 2006).

Sullivan et al. followed up on positive results from a single blind study of nortriptyline (Sullivan et al., 1989) with a double blind placebo-controlled trial of nortriptyline (Sullivan et al., 1993). Six months of severe tinnitus, defined as disruption of daily activities, was required to enter the study. Two of the three following additional criteria also had to be fulfilled for inclusion in the study: (1) a minimum score of three on a zero to seven scale of disability; (2) a score of at least two on a one to five scale of interference of tinnitus on lifestyle; (3) a minimum score of 40 on the disability subscale of the Tinnitus Handicap Questionnaire (Dobie et al., 1993). Tinnitus measures used in the study included the Tinnitus Handicap Questionnaire

(mean scores were 60), participants' response to the question "Has your tinnitus improved?" and tinnitus matching. The Hamilton Rating Scale for Depression (mean score was 17), Hamilton Rating Scale for Anxiety, Beck Depression Inventory, the Multidimensional Pain Inventory (modified for tinnitus to evaluate functional disability) and the Sheehan Disability Scales were the psychiatric and disability measures used. The Hamilton Rating Scales for Depression and Anxiety are interviewer-rated questionnaires. All other questionnaires used were self-report measures. Participants were excluded if they had previously failed an adequate trial of an antidepressant. In total 141 participants were recruited, 117 began treatment and all were regarded by the investigators to have either major depression or depression not otherwise specified (diagnosed by a psychiatrist using the Diagnostic Interview Schedule). The administration of the medication was adjusted to maintain a blood level of 50–150 ng/ml (with a median dose of 100 mg per night) for 6 weeks. Analyses were only run on the 92 subjects that completed the trial. No significant improvement was seen on the Tinnitus Handicap Questionnaire or from the answer to the question "Has your tinnitus improved?" Yet, the participants given nortriptyline had a 6 dB reduction in loudness of their tinnitus in the worst ear at the tinnitus frequency, when adjusted for baseline levels, compared to the placebo group. Also, there was significant improvement in the

Table 1. Double blind placebo-controlled protocols for treatment of tinnitus

Author	Sullivan et al. (1993)	Robinson et al. (2005)	Zoger et al. (2006)	Mihail et al. (1988)
Drug	Nortriptyline	Paroxetine	Sertraline	Trimipramine
Number of weeks of treatment	6	4	16	6
Tinnitus severity required	Yes	No	Yes	No
Minimum tinnitus duration	6 months	6 months	None	None
Percent depressed	100%	<1%	57%	4%
Analysis	Completers only	Last observation carried forward	Completers only	Appears to be completers only
Outcome	6 dB decrease	Aggravation decreased 50 mg subgroup: severity, aggravation, bothered, tinnitus handicap questionnaire subscale 2 decreased, 10 dB decrease	Tinnitus severity questionnaire decreased	8 dB increase

Multidimensional Pain Inventory and the Hamilton Rating Scale for Depression in favor of nortriptyline.

The first trial using a new generation antidepressant used paroxetine (Robinson et al., 2005). The study enrolled 120 participants and the selection criterion was 6 months of daily tinnitus (no specified severity). Paroxetine was titrated from 10 mg per day to 50 mg per day (based on response and side effects, average dose was 41 mg), for an average of 31 days on the maximally tolerated dose of medication. Outcome was evaluated by the Tinnitus Handicap Questionnaire (mean score of 27) and the answer to the questions: "How severe is your tinnitus?", "How aggravated are you by your tinnitus?", "How bothered are you by your tinnitus?" and tinnitus matching. All participants in the study were evaluated by a psychiatrist or masters level clinician using the Structured Interview for the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition), the Hamilton Rating Scale for Depression (mean score of 4 for all participants), Hamilton Rating Scale for Anxiety (mean score of eight for all participants), the Beck Depression Inventory, the Beck Anxiety Inventory, the Symptom Checklist 90-R and the Pittsburgh Sleep Quality Index were completed by those enrolled in the trial. Only one participant in the study was found to have depression. Psychiatric measures used in the study included The Quality of Well-Being Scale, as well as World Health Organization's 5-Item Disability Inventory (all self report measures); 26 participants discontinued the study but 21 of them were still included in the analysis because they provided at least one assessment after taking medication. Analyses were completed on a total of 115 subjects. The most common reason for discontinuation was side effects that included sexual dysfunction, drowsiness and dry mouth.

Results indicated that only one tinnitus measure ("How aggravated are you by your tinnitus?") showed statistically significant improvement. No psychiatric measures or well-being measures showed statistically significant improvement; however, these subjects were not depressed or anxious and therefore it may have been impossible to have

seen a difference in psychiatric measures given a floor effect of their low scores.

However, among the subgroup of participants who reached 50 mg per day as compared to those participants who took placebo, there were numerous positive findings on the following measures: Tinnitus Handicap Questionnaire subscale 2 (hearing ability), the questions: "How severe is your tinnitus?", "How bothered are you by your tinnitus?", "How aggravated are you by your tinnitus?" and a 10 dB decrease in the loudness of the tinnitus based on tinnitus matching.

The most recent of the four double blind studies mentioned above (Zoger et al., 2006) had 76 participants, all of whom the authors judged to be at a high risk for developing severe and disabling tinnitus (based on answering affirmatively to one of the four questions on the Nottingham Health Inventory). All participants except one had tinnitus for less than five years. Tinnitus measures included the Tinnitus Severity Questionnaire, and a visual analog scale of loudness and annoyance in the last week, with references at each end of the scale (e.g., no tinnitus last week). A psychiatrist evaluated all participants in the study using the Structured Interview for the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition). Psychiatric measures included the Hamilton Rating Scale for Depression, the Hamilton Rating Scale for Anxiety, the Comprehensive Psychopathological Rating Scale and Montgomery-Asberg Depression Rating Scale. The Hamilton Rating Scale for Depression and Anxiety where interviewer rated questionnaires and all other questionnaires were self-report measures. Sertraline was started at 25 mg per day and increased to 50 mg per day for 16 weeks. Dropouts were not analyzed. Results indicated a significant decrease in reported tinnitus severity for sertraline compared with placebo based on the Tinnitus Severity Questionnaire and in perceived tinnitus loudness at 16 weeks. Additionally, it was noted that improvements on the Tinnitus Severity Questionnaire were correlated with improvements in depression and anxiety.

A small sample size may have caused inadequate power to detect a difference between the two arms of the study that used trimipramine for tinnitus

(Mihail et al., 1988). Only 26 participants were enrolled in this cross-over trial. The selection criteria for the study did not include the duration or the severity of the tinnitus. The only inclusion criterion was tinnitus that failed other treatments. Only tinnitus matching and a seven-point tinnitus-severity scale were used to determine the effect of the medication. Psychiatric measures used included the Zung Depression Inventory (although no scores were given, it was reported that only one participant was depressed) and the Million Behavioral Health Inventory. Although the original article states 150 mg four times a day of trimipramine was prescribed for 6 weeks, this greatly exceeds the maximum recommended dose in the package insert and the article states the medication was given due to its sedative effects, implying night time dosing of medication, not four times a day dosing. A recent meta-analysis of antidepressants for tinnitus reports the dose of medication for the trial was 150 mg per day (Baldo et al., 2006). Based on percent improved using the severity scale, there was no difference between effect of the drug and of placebo. However, there was an 8 dB intensity increase in the tinnitus from treatment with trimipramine and no change in the intensity of the tinnitus with placebo, a statistically significant finding of worsening with trimipramine.

In addition to these four double blind studies, many published case reports have shown beneficial effects of treatment with antidepressants, such as amitriptyline, fluoxetine, paroxetine and venlafaxine on tinnitus (Koshes, 1992; Shemen, 1998; Christensen, 2001; Anonymous, 2006). A single blind study of amitriptyline (Bayar et al., 2001) and nortriptyline was published (Sullivan et al., 1989); both trials found reduced subjective complaints from tinnitus and a decrease in the intensity of the tinnitus based on loudness matching. A study of the effect of amitriptyline that did not specify if it was single or double blind (but appears to be single blind because the conditions were drug, placebo, biofeedback or sham biofeedback) has been published (Podoshin et al., 1989) showing subjective improvement greatest for biofeedback followed by amitriptyline followed by placebo and sham biofeedback. A retrospective chart review (Folmer et al., 2002) found support for

antidepressants having a beneficial effect on tinnitus. These reports were reviewed in more detail by Robinson and Viirre (Robinson et al., 2006).

Synthesis of evidence for antidepressants benefiting tinnitus

Overall, tinnitus in depressed patients appears more responsive to antidepressants than in non-depressed patients. This finding is supported by the results of the nortriptyline trial (Sullivan et al., 1993), where all participants were either considered to have major depressive disorder or depression not otherwise specified, and the sertraline study (Zoger et al., 2006) where participants in the drug group had Hamilton Depression Rating Scale scores of 20 and those in the placebo group had an average of 22 (both indicative of clinically significant depression). Compare those score with the scores from the paroxetine investigation (Robinson et al., 2005) where the average Hamilton Depression Rating Scale score was five for the drug group and four for the placebo group (within the range of the normal population).

In a similar way, anxious patients with tinnitus appear more likely to benefit from treatment with antidepressants than non-anxious patients. Although the nortriptyline study did not specifically assess anxiety, the later trials did. In the sertraline study, both the drug group and the placebo group had a clinically significant level of anxiety (Zoger et al., 2006), compared to the paroxetine investigation where neither the drug or placebo group had a clinically significant level of anxiety (Robinson et al., 2005). The nortriptyline and sertraline trials where the patients were more depressed and/or anxious had more positive results than the trimipramine or paroxetine studies where the patients were generally not depressed and/or anxious.

Outcome of studies using antidepressants also depends on the severity of tinnitus, and participants who have more severe tinnitus show greater response to treatment. The nortriptyline trial had Tinnitus Handicap Questionnaire mean of 38 for the drug group and 44 for the placebo group, and

the values were 29 and 27, respectively, for the paroxetine study. The sertraline investigation did not use the Tinnitus Handicap Questionnaire. The nortriptyline and the sertraline experiments both required the patients to have a certain severity or be at high risk for developing severe tinnitus (disruption in daily activities or answering affirmatively to one of the four questions on the Nottingham Health Inventory, respectively) in order to enter the research protocol, but no such entry criteria was required for the trimipramine or paroxetine investigations. The nortriptyline and sertraline trials, where patients had more severe tinnitus, showed more positive results than the trimipramine or paroxetine studies in which the patients were not required to have a specified level of severity to enter the trial.

Of those who are responsive to treatment of tinnitus with antidepressant medications, onset of improvement with antidepressants has been reported to occur as early as 1 week (Shemen, 1998). However, in the double blind placebo-controlled studies, improvement was only reported at the end of each protocol (4 weeks for the paroxetine trial, 6 weeks for the nortriptyline trial, 16 weeks for the sertraline trial) and it is unclear if improvement may have occurred prior to that time. The longer duration of treatment in the nortriptyline and sertraline investigations may account for more improvement being seen in those experiments compared to the paroxetine research where treatment was for 4 weeks.

Based on the lack of uniformity in the above studies, it cannot be predicted how long it will take tinnitus to respond to treatment with an antidepressant. Perhaps the 4-week duration of the paroxetine trial was not long enough to see a benefit. It is known that different disorders require different amounts of time to respond to antidepressants. For example, depression usually responds within 4 weeks to a dose of medication but obsessive compulsive disorder often requires a longer duration in order to see an improvement (Jenike, 2004).

Using adequate dosing of medication is important to achieve the best results. In the paroxetine study, the subgroup that reached the highest dose of medication saw improvements, yet the overall

group did not. Dosing may have been an issue in the single blind biofeedback vs. amitriptyline research as well. The dose of amitriptyline used was 10 mg tid and although amitriptyline showed greater improvement than either placebo or sham biofeedback, biofeedback showed greater improvement than amitriptyline. However, the dose of amitriptyline was much lower than the standard dose of 150 mg per day used for depression. It is also certainly possible that the dose of medication required for effective treatment of tinnitus is not the same as that required for the treatment of depression. This discrepancy in dosing is well known when comparing depressive and anxiety disorders; depression responds to lower doses of medication than obsessive compulsive disorder (Jenike, 2004).

Mechanisms of action for antidepressants causing tinnitus

Given that antidepressants have been reported to both cause and help tinnitus, the precise mechanism of action is difficult to ascertain. It is unknown if either outcome is due to the direct effect of the antidepressants on the brain via serotonin, or due to ancillary binding properties of antidepressants. What is known is that the auditory cortex and auditory nuclei are rich in serotonin receptors (Simpson and Davies, 2000). Variations of the promoter region of the 5-hydroxytryptamine transporter gene are associated with differences in auditory evoked potentials in healthy controls (Gallinat et al., 2003). Serotonin is also known to modulate auditory information directly in the cochlear nucleus (Ebert and Ostwald, 1992) and the inferior colliculus (Hurley, 2006), as well as in the amygdala (Stutzmann et al., 1998). The latter is thought to be involved in assigning affective significance to auditory information. The complexity of this area is demonstrated by the fact that 5-HT_{1A} agonist can cause both increases and decreases in excitability on different cells in the inferior colliculus (Hurley, 2006) and cochlear nucleus (Ebert and Ostwald, 1992).

Mechanisms of action for treating tinnitus with antidepressants

Improvements in tinnitus that occur with the administration of antidepressants could be due to an indirect effect on tinnitus such as improvements in depression or anxiety disorders. This hypothesis would be supported by the research that shows individuals with tinnitus, who are depressed, improved with regard to their tinnitus when given antidepressants, as well as a retrospective chart review (Katon et al., 1993; Folmer et al., 2002; Zoger et al., 2006).

It is also possible that improvements in tinnitus may be the result of a direct effect of antidepressants. As described in the section above, it is unclear at this stage of research whether the serotonergic properties of antidepressants would lead to improvements in tinnitus given the complex nature of their effects in the entire auditory pathway. The mechanism of improvement in tinnitus as a direct effect of serotonin binding seems to be supported by the paroxetine investigation because in this trial the participants were not depressed and those who took 50 mg per day still had improvements in tinnitus (Robinson et al., 2005).

Anticholinergic side effects are common with antidepressants (especially tricyclic antidepressants) and it is necessary to consider a cholinergic mechanism for tinnitus or anticholinergic mechanism for improvement in this symptom. Muscarinic acetylcholine receptors are found in the cochlear nucleus, superior olive and inferior colliculus (Glendenning and Baker, 1988).

Systemic injection of scopolamine, a muscarinic antagonist, decreases salicylate-driven plasticity in the auditory cortex (Wallerhausser-Franke et al., 2006). Choline acetyltransferase activity (responsible for the synthesis of acetylcholine from choline and acetyl coenzyme A) increases in multiple areas and layers of the cochlear nucleus on the side of noise exposure (Jin et al., 2006). Muscarinic acetylcholine receptor binding is greater ipsilaterally in the cochlear nucleus after unilateral cochlear ablation (Jin and Godfrey, 2006). These studies indicate an increase in the synthesis of acetylcholine and receptor activity after noise exposure. Therefore, it would be reasonable to hypothesize

that an anti-cholinergic agent may be able to prevent tinnitus after damage to the auditory nerve, regardless of the origin of that damage.

Conclusions

Some antidepressants are reported to cause tinnitus and other antidepressants appear to have beneficial effects on tinnitus. At present, no particular antidepressant or class of antidepressants has been identified as more likely to have tinnitus as a side effect or more likely to be beneficial for this condition.

The results of double blind placebo-controlled trials in different patient populations (patients with or without severe tinnitus, tinnitus patients with or without co-morbid depression) and with different drugs (trimipramine, nortriptyline, paroxetine and sertraline) have yielded different results. However, there is an indication that antidepressant treatment is worth trying in patients with severe tinnitus and especially in patients with co-morbid depression or anxiety who understand the risks and benefits of taking antidepressants, as well as the off-label use of the medication.

It is essential that studies measure depression and anxiety with validated instruments pre- and post-treatment. The standard psychiatric assessment is the interviewer-rated Hamilton Rating Scale for Depression, and this was used in three of the four double blind placebo-controlled trials reviewed above. It is recommended that researchers stratify for the presence and absence of current major depressive episode or current anxiety disorder, other than not otherwise specified diagnoses, and enroll an adequate number of participants in each arm of the study to detect a difference between arms. Patients with depression and anxiety not otherwise specified are quantitatively and qualitatively different from those meeting criteria for a major psychiatric disorder, and therefore should not be lumped with those participants who meet a major psychiatric disorder. Depression (or anxiety), not otherwise specified, is defined as a depression (or anxiety) that is causing significant impairment or distress but does not meet criteria for major depression or a specified anxiety

disorder (e.g. panic disorder, generalized anxiety disorder, obsessive compulsive disorder, post traumatic stress disorder, social phobia) and is not due directly to a medical condition or substance (e.g. street drug, alcohol or prescribed medication).

An adequate dose of medication for a sufficient duration of time is also important in determining if an antidepressant medication is effective for tinnitus. Without these two things it cannot be determined whether negative results are simply the product of under-treating the patient. In treatment of depression or anxiety disorders, psychiatrists do not consider a drug a failed trial until the dose has been increased to a dose higher than the lowest dose approved by the FDA and the patient has been on the medication for at least 2 months at this higher dose. Given that we do not know how long it takes tinnitus to respond to antidepressants, it would be important to have a monthly assessment of the patient for 6–12 months. Additional recommendations include, after discontinuation of medication (remember not to do this abruptly in order to prevent serotonin withdrawal syndrome) continue to follow the patient on a monthly basis to see if the tinnitus returns. This will provide you with an indication whether medication will need to be continued for life or could be given for a few months and have a permanent effect.

Abbreviations

DSM IV	diagnostic and statistical manual of mental disorders fourth edition
FDA	food and drug administration
5-HT	serotonin
SNRI	serotonin and norepinephrine reuptake inhibitors
SSRI	selective serotonin reuptake inhibitors

Acknowledgments

I would like to acknowledge Dr. Marc Schuckit for his advice and editing of this chapter, and

Dr. Erik Viirre and Dr. Murray Stein for their collaboration and mentorship regarding my research with antidepressants and tinnitus.

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CHAPTER 25

Treatment of tinnitus with acamprosate

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Abstract: Acamprosate, a drug used to treat alcohol dependence, was first reported as a potential treatment for tinnitus in 2005. The drug may improve tinnitus by a dual mechanism of action, acting both as a glutamate antagonist and as a GABA agonist. It is suggested that its action may be both on the ear and the nervous system.

Keywords: tinnitus; acamprosate; NMDA

Introduction

Many studies have shown that approximately 90% of patients with tinnitus have hearing loss, which implies that some cochlear damage is involved, at least in early stages of its development (Bonfils and Puel, 2001; Eggermont, 2003; Azevedo and Figueiredo, 2004). Many of the neurotransmitters that are involved in sensory transduction in the cochlear, such as glutamate, GABA, and dopamine, also play a neurotransmitter role in central auditory pathways. This suggests that drugs acting on these neurotransmitter systems may be able to modulate the activity of both peripheral and central auditory pathways (Azevedo and Figueiredo, 2004; Figueiredo and Azevedo, 2004).

The arsenal of drugs that can alleviate tinnitus has grown in the last years, by inclusion of drugs such as gabapentin (Bauer and Brozoski, 2006) (Chapter 27), piribedil (Hastak, 2003) and, more recently, acamprosate (Azevedo and Figueiredo, 2005), a drug originally developed for the

treatment of alcohol dependence that was reported to have potential benefit for the treatment of tinnitus in 2005.

The first study published with acamprosate in tinnitus showed encouraging results, with 89% of treated patients reporting relief of symptoms using a ten-point visual analogue scale (VAS). The beneficial effect of acamprosate may be explained by its action as an NMDA glutamate receptor antagonist and an agonist of GABA_A receptors allowing it to decrease excitatory glutamic activity and enhance inhibitory GABAergic activity in auditory pathways (Pierrefiche et al., 2004; Azevedo and Figueiredo, 2005).

The role of neural transmitters in tinnitus

Of the many theories that have attempted to explain the physiopathology of tinnitus, one of the most appealing is the excitotoxic theory postulating that over-release of glutamate in peripheral and central auditory pathways synapses leads to hyperactivation of NMDA receptors as well as an increase in their expression (Pujol et al., 1993). This triggers excessive entry of calcium into the

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primary auditory neurones, with subsequent osmotic swelling and cell lysis. Neurons in which NMDA receptors are over-expressed are more sensitive to the excitotoxic effects of glutamate. In this way, a “vicious circle” is set up, which can propagate throughout the auditory pathways (auditory pathway epilepsy) (Puel et al., 1998). The actions of neural transmitter that may be involved in tinnitus are reviewed by Eggermont in Chapter 2.

Acamprosate

Acamprosate (calcium acetylhomotaurinate or calcium acetyl-amino-propano-sulfonate) has a chemical structure, which is analogous to that of certain amino acid transmitter substances, such as GABA, glutamate, and taurine. The mechanism of action of acamprosate involves effects on both the excitatory glutamic system and the inhibitory GABAergic system. Acamprosate increases the number of reuptake sites for GABA and modifies GABA reuptake in rats increasing GABAergic transmission, which inhibits the activity in the auditory pathways. Acamprosate also attenuates glutamic neurotransmission, especially that mediated by NMDA receptors, probably due to an effect on calcium conductance (Pierrefiche et al., 2004; Azevedo and Figueiredo, 2005).

Since both GABAergic and glutamic mechanisms may be involved in the development or expression of tinnitus, acamprosate is a promising candidate for treatment of some forms of tinnitus. No other drug that has a concomitant action on both of these neurotransmitter systems is known to be used in treatment of tinnitus (Azevedo and Figueiredo, 2005).

Material and methods

The first (and only) published clinical study evaluating the use of acamprosate in tinnitus, was carried out in Volta Redonda, a city of 300,000 inhabitants in the state of Rio de Janeiro, Brazil (Azevedo and Figueiredo, 2005). The city has a large population of patients with tinnitus, due to the fact that it has a big steel industry and also is home to many retired people. Noise-induced

hearing loss and presbycusis are the main causes of tinnitus in Volta Redonda (Fig. 1).

In our study, 50 patients with sensorineural tinnitus were selected. Two participants (4%) had normal hearing, 30 (60%) had mild hearing loss, 10 (20%) had moderate, 6 (12%) had severe, and 2 (4%) had profound hearing loss. The inclusion criteria were normal otoscopy, absence of temporomandibular joint disease, and absence of middle ear disease. We also excluded individuals with muscular tinnitus and TMJ disorders although such individuals may have sensorineural tinnitus. The sample was randomized to one of two treatment groups, 25 patients taking placebo three times a day and 25 taking acamprosate 333 mg three times a day for 3 months in a double-blind study. The treatment group and the control group were matched with regards to age, gender, and hearing loss. The participants gave informed consent.

The reason that a dose of only half of the recommended dose for treatment of alcohol dependence was used was to reduce the risk of side effects, such as epigastralgia and flatulence.

At inclusion, each group was asked to rate their tinnitus according to loudness and annoyance using a ten-point VAS. After 3 months, both groups rated their tinnitus again.

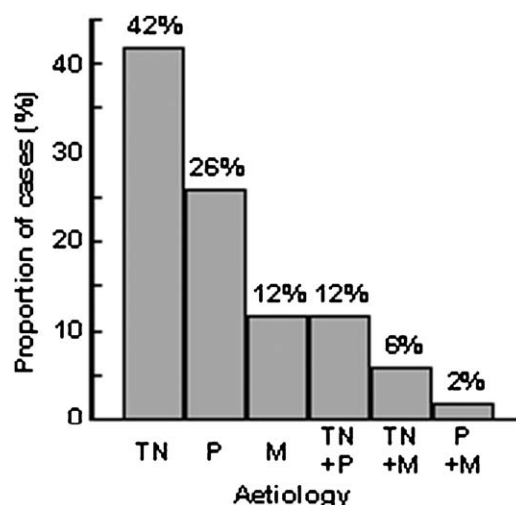


Fig. 1. Probable causes of tinnitus in 50 participants in Volta Redonda study. TN: traumatic noise; P: presbycusis; M: metabolic cause.

Results

The number of patients with any improvement (greater than zero) in VAS at day 90 in the group treated with acamprosate (86.9%) was significantly higher ($p = 0.004$; Student's t -test) than in the group treated with placebo (44.4%). The number of patients reporting an improvement at 90 days of $\geq 50\%$ was also significantly ($p = 0.012$) higher in the group treated with acamprosate (47.8%) than in the group treated with placebo (11.1%). No patient in the group treated with acamprosate reported worsening of the tinnitus score. Three patients (13.1%) reported no improvement, nine (39.1%) had improvements of less than 50%, and eleven patients (47.8%) had improvements that were larger than 50%, including three participants (13.1%) who reported that tinnitus had disappeared completely.

The extent of improvement was significantly ($p = 0.0001$) higher in the acamprosate group (mean of improvement: 51.1%) than in the placebo group (mean of improvement: 10.8%). To assess the progression of tinnitus score over time separately for each group, a Friedman Variance Analysis (two-way Analysis of Variance by Rank) was performed (Fig. 2).

No statistically significant influence of age, gender, aetiology, duration and type of tinnitus, extent of hearing loss or audiometric features was observed on tinnitus scores in either the acamprosate or the placebo group.

The side effects reported with acamprosate were mild (epigastralgia, choking). No statistically

significant difference in side effects ($p = 0.35$; Fisher's exact test) between the groups receiving acamprosate (12%) and placebo (20%) was observed.

Discussion

The reason for the beneficial effect of acamprosate may be its combined effect on NMDA and GABA receptors. Drugs that affect GABA receptors such as benzodiazepines have been found beneficial in some patients with tinnitus (see Chapter 2) (Vernon and Meikle, 2003), but acamprosate is probably the first drug with effect on NMDA receptors that has been found effective in treatment of tinnitus. It has been claimed that the effect of salicylate in causing tinnitus is related to its augmentation of the NMDA receptor (Guitton et al., 2003) (see Chapter 2). It therefore seems reasonable to suggest that suppression of the NMDA receptor may alleviate tinnitus through its suppression of NMDA receptors. However, Flupirtine, an NMDA antagonist with many claimed medical use, has been found ineffective in treatment of tinnitus, (Salembier et al., 2006).

Acamprosate was originally developed as an analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Early studies of the mechanism of action of acamprosate focused on the GABAergic system. This approach was justified by the known implication of GABA receptors in the acute and chronic effects of alcohol on the central nervous system (Morrow, 1995; Matthews et al., 1998) and by the structural similarity of acamprosate with GABA.

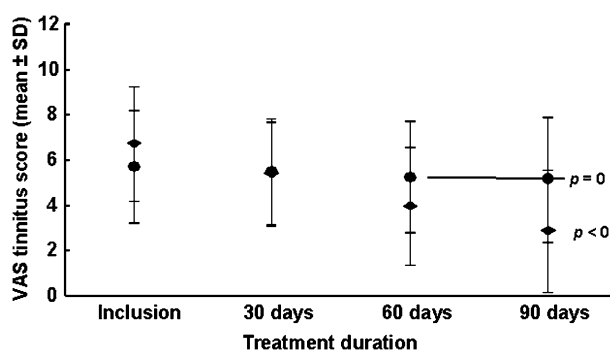


Fig. 2. Evolution of tinnitus score over the course of the study. VAS: visual analogue scale; ●: placebo group; ◆: acamprosate group.

However, acamprosate has little in common with other drugs that facilitate GABAergic transmission such as barbiturates or benzodiazepines. Recent investigations of acamprosate in a variety of neuronal preparations have not revealed any evidence for a direct interaction of this drug with GABA_A receptors (Zeise et al., 1990).

Effects of acamprosate on uptake of GABA into brain preparations have also been investigated, though with an ex vivo rather than in vitro design (Daoust et al., 1990). Effects of acamprosate treatment were complex, with inhibition in some brain areas, potentiation in some, and no effects in others, depending on dosing and concomitant ethanol exposure. One of the most convincing study concerning the GABA neurotransmitter was performed by Dachour and De Witte (1999) using brain microdialysis technique where he demonstrated an increase of GABA in the nucleus Accumbens in alcoholized rats treated by 400 mg/kg/day of acamprosate during 4 weeks (Dachour and De Witte, 1999).

On the other hand, there is clear evidence for a decrease in excitatory amino acid-mediated neurotransmission through a direct interaction of acamprosate with NMDA receptors (Zeise et al., 1993).

The effects of acamprosate on GABAergic neurotransmission observed previously would thus be secondary to the effect on NMDA receptor-mediated neurotransmission.

In the dosage of acamprosate used in this study, the side effects reported for higher dosages (effect on blood pressure, insomnia, and impotence) were not observed. It is interesting that the effect of the drug is delayed at least 1 month and that the beneficial effect increases steadily from 1 month to the end of this study (3 months). The reason for this delayed effect is not known may resemble the effect of SSRI treatment of depression. The experience from this study, however, emphasize that the duration of studies of pharmacological treatment of tinnitus should last at least 3 months and preferably longer.

Conclusion

In conclusion, acamprosate is a potentially interesting drug treatment of tinnitus. The pilot study

has shown promising results but several questions remain to be answered by further and larger studies. For example, it is important to ascertain whether the observed improvement in tinnitus score persists beyond 3 months of therapy. In the present study, the effects of acamprosate on tinnitus could not be evaluated over a longer period since the drug is no longer commercially available in Brazil. In addition, it would be interesting to see if the treatment effect could be increased by using a higher dose of acamprosate, such as that used in the treatment of alcohol dependence.

Acknowledgments

To Matteo de Nora, for ideas and support, to everyone at Tinnitus Research Initiative, especially Juan Miguel Lainez, Berthold Langguth and Ulli Soltani. To Aage Møller, for the concept of this book, to Rémy Pujol and Jean-Luc Puel from Montpellier, to Nuno Trigueiros Cunha from Porto and to Tanit Sanchez, from São Paulo. To everybody at OTOSUL and our parents and children.

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CHAPTER 26

Zinc as a possible treatment for tinnitus

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Abstract: Zinc is an essential trace element present in all organs, tissues, fluids, and secretions of the body and it is widely distributed in the central nervous system, including the auditory pathway in synapses of the VIII nerve and in the cochlea. Zinc is an essential component of Cu/Zn superoxide dismutase (SOD) and in certain enzymes and it is important for proper function of the immune system. Three possible mechanisms have linked zinc to tinnitus; cochlear Cu/Zn SOD activity, synaptic transmission, and depression. Evidences in the literature suggest prevalence rates of zinc deficiency in individuals with tinnitus from 2 to 69%, affecting elderly individuals more frequently. Four among five small studies indicate that administration of zinc has a beneficial effect on tinnitus but these results still have to be confirmed in clinical trials with larger samples using a cross-over design, validated tinnitus handicap questionnaires, measurements of tinnitus magnitude, and accessing the coexistence of other symptoms such as depression, phonophobia, and hyperacusis.

Keywords: zinc; deficiency; hypozincemia; tinnitus; mineral supplements

Introduction

The use of zinc as a medical treatment was mentioned as early as ~1500 BC in the Ebers' papyrus where the topical use of zinc as calamine was recommended to heal lesions around the eye (Cassel, 1978). It has also been cited in *Charaka Samhita*, an ancient Indian manuscript from 1000 BC. Since those days it has been used in preparation of topical medicines for skin and eyes. In the late 1700s and early 1800s in Western Europe, zinc oxide and zinc sulfate were administered for the treatment of convulsions, urethral discharge, and vaginal exudates. The use became unpopular because of the variability of chemical composition of the available compounds and the lack of efficacy (Barceloux, 1999).

Zinc, an element that is present in all organs, tissues, fluids, and secretions of the body, is essential to human homeostasis. Over 300 enzymes require zinc for their function (Valee and Auld, 1993). Zinc is involved in the synthesis and stabilization of proteins, of deoxyribonucleic acid (DNA), and ribonucleic acid (RNA), and it plays a structural role in the function of ribosomes and membranes. It also has essential functions in reproduction, bone formation, growth, wound healing, signaling in the nervous system, and in behavioral responses (Russell, 2005).

Zinc is also a structural component (along with copper) of superoxide dismutase (Cu/Zn SOD), that has a vital anti-oxidant role and important for human health in general, being among the first line of defense in the detoxification of products resulting from oxidative stress (Johnson and Giulivi, 2005).

The brain has the highest zinc content in the body, estimated to ~150 µmol/L (~10 times higher

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than serum zinc levels) (Takeda, 2000). Zinc can enter the brain through the blood-brain and blood-cerebrospinal fluid barriers (Takeda, 2001). Zinc homeostasis is maintained by brain capillary endothelial cells (Lehmann et al., 2002). Uptake of zinc from extracellular fluids by neurons and glial cells is controlled by zinc transporters (Mocchegiani et al., 2005).

Zinc-sensitive targets have been identified within the central nervous system (e.g., gamma amino-butyric acid (GABA), AMPA, *N*-methyl-D-aspartate (NMDA), acetylcholine, serotonin, glycine, glutamate, dopamine, calcium, potassium, and sodium). (For a review see Frederickson et al., 2005.) These investigators suggested that the zinc atom is so ubiquitous in cellular metabolism, that even minor decrease in the availability of zinc in the CNS may have several biological and clinical effects. Zinc is mainly present in synaptic vesicles of glutamatergic neurons and may serve to modulate post-synaptic activity of many neurotransmitters including excitatory and inhibitory receptors, particularly the NMDA and GABA receptors (Cuajungco and Lees, 1998) and probably also modulation of glycinergic synaptic transmission (Laube, 2002).

Specifically, zinc has been shown to modulate synaptic function in the cochlear nucleus through its involvement with glutamate receptors (Zirpel and Parks, 2001). In the cochlea, zinc is an essential component of Cu/Zn SOD, which is the most abundant antioxidant enzyme in the cochlea and provides a first line of defense against free radical damage. The high rate of metabolic activity and generation of reactive oxygen species (ROS) in the cochlea (Rarey and Yao, 1996) may explain the abundance of this enzyme in cochlear tissues. Cu/Zn SOD deficiency potentiates cochlear hair cell degeneration, probably through metabolic pathways involving ROS (McFadden et al., 1999).

Zinc deficiency

Numerous age-related declines in neuronal function have been related to a reduction in intracellular or extracellular zinc ion availability (Mocchegiani

et al., 2005). Zinc deficiency is particularly prominent in elderly people, probably due to poor uptake (DeBartolo, 1989; Ochi and Eggermont, 1997; Prasad, 1993; Yetiser et al., 2002).

Zinc deficiency is associated with growth retardation, anorexia, delayed sexual maturation, iron-deficiency anemia, and alterations of taste (Prasad, 1991). Clinical manifestations include diarrhea, alopecia, muscle wasting, depression, irritability, and a rash involving the extremities, face, and perineum (Russell, 2005). Plasma zinc concentrations are maintained without notable change when zinc intake is restricted or increased unless these changes in intake are severe and prolonged (Cousins, 1989). Therefore, zinc plasma levels not always correlate with intracellular and overall body stores and zinc plasma levels may be within the normal range while an overall zinc deficiency exists (Johnson et al., 1993). Normal serum zinc levels range from 75 to 120 mg/dL (Russell, 2005).

Zinc is present in relatively high concentrations in meat, seafood, dairy products, nuts, legumes, and whole grains (Prasad et al., 1963; Barceloux, 1999). The recommended dietary allowance for adults is 8 mg/day for women and 11 mg/day for men. The tolerable upper intake level for adults is 40 mg/day, according to the Food and Nutrition Board from the Institute of Medicine in the US.

Zinc deficiency among tinnitus patients

Published results regarding the prevalence of hypozincemia among individuals with tinnitus varies widely (Fig. 1) in studies with 30–78 participants. Some investigators found average zinc levels of 88 mg/dL in a study of 73 individuals with tinnitus (Ochi et al., 2003); and in 38 non-tinnitus controls the average level was 92 mg/dL but the difference between tinnitus patients and normal controls was not statistically significant ($p = 0.06$). Twenty-four of the 73 individuals with tinnitus had levels that were more than 1 standard deviation lower than in the normal group. While zinc deficiency increases over age 60 years (Shambaugh, 1986), this study (Ochi et al., 2003) had excluded participants older than 59 years. They performed

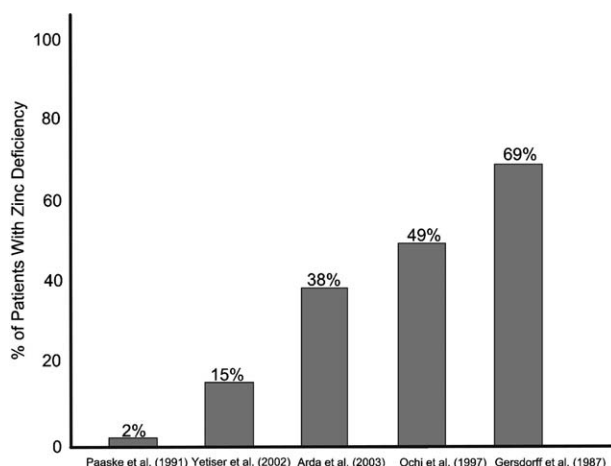


Fig. 1. Prevalence of hypozincemia among tinnitus patients.

loudness matches and found statistically significant louder tinnitus in those patients with zinc deficiency than in those tinnitus patients with zinc level within normal limits.

Anatomical location of the influence of zinc on tinnitus

In the cochlea

Zinc is particularly important for the normal function of the stria vascularis because it is a component of Cu/Zn SOD, and as a trace element. This is one way zinc deficiency may affect tinnitus. Administration of zinc may therefore have a protective effect on cochlear cells and other structure damage oxidative substance. Zinc's contribution to the integrity and activity of Na, K ATPase (ion-transporting enzyme, Na^+ , K^+ — adenosine triphosphate) (Rarey and Yao, 1996), and its general stabilizing effect on cochlear biochemistry reduces some forms of tinnitus.

Neurotransmission

Zinc modulates both excitatory and inhibitory neurotransmission and it may thereby affect tinnitus. Zinc influences particularly glutamatergic synaptic transmission and the binding of peptides and other

ligands to their neuroreceptors (Frederickson, 1989; Takeda, 2000). Zinc directly inhibits excitatory NMDA receptors and potentiates inhibitory transmission mediated GABA_A receptors (Smart et al., 2004). Frederickson et al. (2005) have stated “that the dominant effect of zinc in the normal brain is to reduce excitability, thereby functioning as an endogenous anticonvulsant” (p. 453). It is likely that some forms of tinnitus is caused by an increase in spontaneous neural activity, and zinc deficiency that may lead to increased neural firing could therefore be involved in generating tinnitus (Prasad, 1993).

Depression

There is evidence that depression often accompany tinnitus (Chapter 20). In the general population, estimates of depression ranges from 2 to 5% (Weissman and Bruce, 1991). The coexistence of tinnitus and depression occurs in ~30–69% (Simpson et al., 1988; Sullivan et al., 1988; Erlandsson et al., 1991; Holgers et al., 1990; Satoh et al., 1998; Zoger and Svedlund, 2002; Folmer and Shi, 2004). Experiments with animal models of depression have shown that zinc can provide an antidepressant-like effect (Nowak et al., 2005) and studies in patients with unipolar depression who are treated by standard antidepressant therapy have

significantly reduced scores on depression scales when receiving zinc in addition to the standard treatment when compared to individuals receiving placebo (Nowak et al., 2003). The mechanisms of the antidepressant activity of zinc might be related to zinc's direct antagonism of NMDA receptor, its antagonistic action on group I metabotropic glutamate receptors, or by potentiation of AMPA receptors, which both attenuates the NMDA receptor function (Nowak et al., 2005). Patients presenting tinnitus and depression might therefore particularly benefit from administration of zinc.

Evaluation of zinc for treatment of tinnitus

The results of different studies evaluating the results of studies of administration of zinc for treatment of tinnitus are shown in Table 1.

Administration of zinc

Zinc deficiency may be treated with orally administered elemental zinc, 60 mg twice a day (Russell, 2005). For treatment of tinnitus, the adequate dosage of zinc is yet to be determined. Most studies that have shown benefit from administration of

zinc (Gersdorff et al., 1987; Paaske et al., 1991; Ochi et al., 1997; Yetiser et al., 2002; Arda et al., 2003) (Figs. 2–4), have used 50–66 mg of elemental zinc daily (some use once a day others three times a day, but the total amount is between 50 and 66 mg daily). Arda et al. (2003) demonstrated that zinc blood levels increased significantly after administering a dose of 50 mg once a day of elemental zinc for 2 months without major adverse effects.

Zinc is generally well tolerated and the most common side adverse effects are maldigestion, abdominal pain or nausea, leukopenia, neutropenia, sideroblastic anemia, etc. It has to be administered with caution in individuals presenting low blood copper levels since they have an increased risk to develop hematologic abnormalities. Because copper and zinc are both absorbed in the stomach and proximal duodenum, excessive serum zinc levels might cause an up-regulation of metallothionein synthesis (an intracellular ligand) in the enterocytes. Copper has a higher affinity for metallothionein than zinc, remaining in the enterocytes, being lost in the feces as the intestinal cells dies off (Fischer et al., 1983). This action on absorption might cause a “zinc-induced” copper deficiency. Also iron supplements, folic acid, oral

Table 1. Studies on tinnitus and zinc

Authors	N	Zn dosage (mg/daily)	Period of treatment (months)	Results	Measurement	Comments on study design
Gersdorff et al. (1987)	30	60	1	14/30 Improved	Six categories	One treatment group
Paaske et al. (1991)	48	66	2	Not significant	10-point scale	Treatment/ placebo
Ochi et al. (1997)	11	34–68	2 Weeks	Statistically significant improvement	11-point scale	One treatment group; only treated zinc-deficient
Yetiser et al. (2002)	40	50	2	58% all patients improve (not significant); 82% elder patients improve (significant)	10-point scale	One treatment group
Arda et al. (2003)	41	50	2	Statistically significant improvement in treatment but not placebo group	7-Item questionnaire	Treatment and placebo

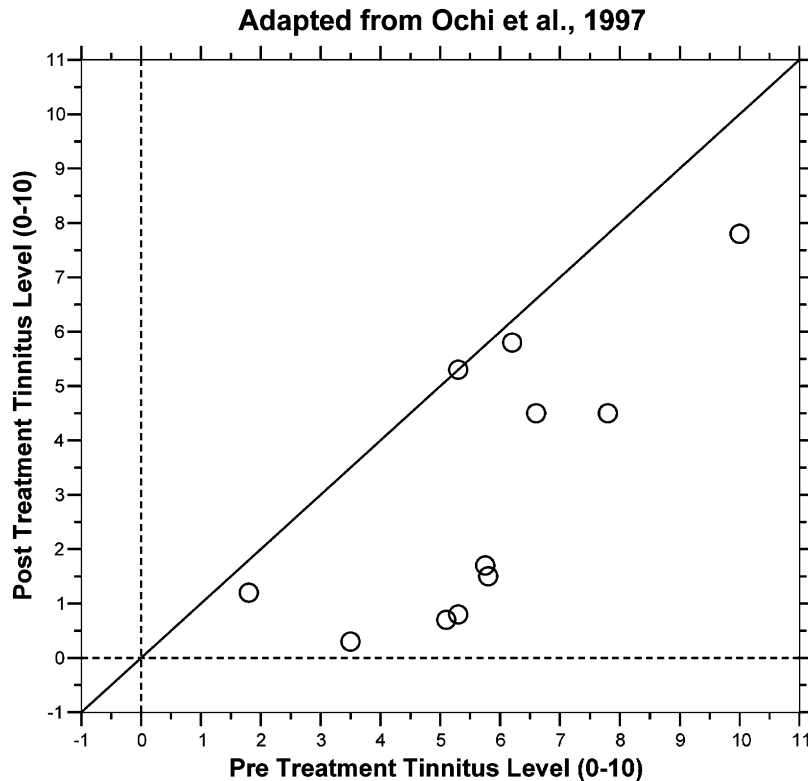


Fig. 2. Pre and post treatment tinnitus measurements observed by [Ochi et al. \(1997\)](#).

penicillamine, phosphorus-containing preparations, tetracycline, or fluoroquinolone antibiotics might interfere with zinc absorption. Fiber containing foods, milk, poultry, grains, and coffee should be avoided or taken 2h after taking zinc ([USP DI[®] Drug Info, 2006](#) and [Yetiser et al. \(2002\)](#) suggest that elderly, or those who are zinc deficient, are more likely to show a benefit from zinc. [Seidman and Babu \(2003\)](#) suggest that patients with recent-onset tinnitus are the best candidates for zinc. The effect symptoms that often accompany tinnitus such as depression, phonophobia, and hyperacusis have not been considered in studies of the benefit from administration of zinc.

Concluding remarks and future perspectives

Zinc plays a critical role in several aspects of cochlear and neuronal function and zinc deficit has

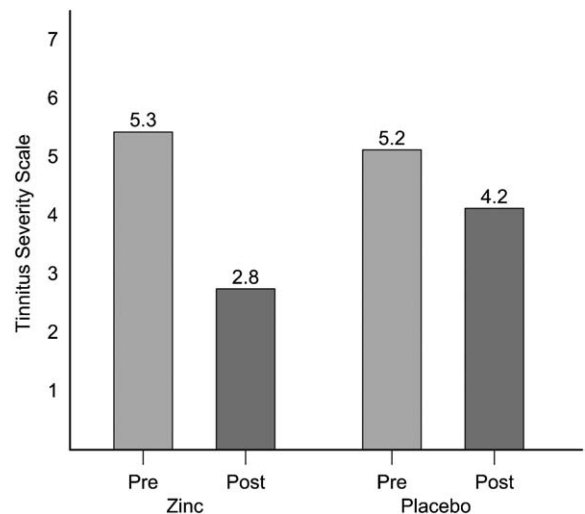


Fig. 3. Improvement on Tinnitus Severity Scale observed by [Arda et al. \(2003\)](#).

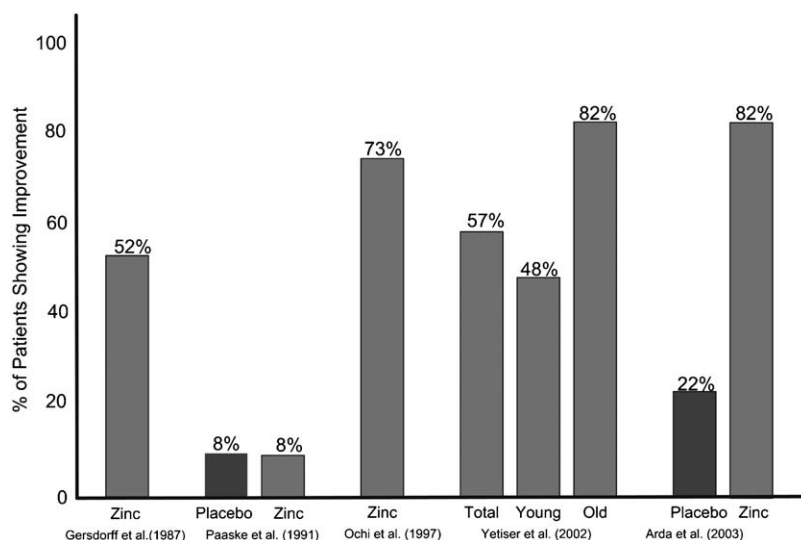


Fig. 4. Zinc treatment results from several published studies.

been implicated in tinnitus. Several independent preliminary trials support the effectiveness of zinc, but these promising results suffer from a lack of adequate design and require confirmation by a well-designed trial. However, these and other observations highlighted in this review suggest that administration of zinc may be beneficial to individuals with some kind of tinnitus and that it will relieve tinnitus and may even prevent it. Aside from its likely beneficial effect on some forms of tinnitus, zinc is useful in preserving good health, particularly in the presence of marginal zinc deficiency, which is common in the elderly (Vaquero, 2002).

Acknowledgment

This work is partially supported by a grant provided by Tinnitus Research Initiative and NIH grant R01 DC00597201A1.

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CHAPTER 27

Gabapentin

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Abstract: Several lines of evidence suggest that loss of central inhibition after deprivation of input from the ear (peripheral deafferentation) may be one cause of chronic tinnitus. Aging and acoustic trauma, the two most common causes of peripheral damage to the auditory system, each decrease input to central auditory structures. Loss of input to tonic inhibitory systems would release excitatory structures from inhibitory regulation. The increased activity resulting may be interpreted by more rostral structures in the auditory pathway as tinnitus. Down-regulation of γ -amino butyric acid (GABA), a major inhibitory neurotransmitter of the central auditory pathway, is a potential mechanism for the loss of inhibition. Both animal studies and human clinical trials implicate loss of inhibition, and specifically loss of GABA function, in the development of acoustic trauma-induced tinnitus.

Keywords: tinnitus; acoustic trauma; GABA; gabapentin; vigabatrin; inhibition; clinical trial; animal model

Introduction

It has been hypothesized that partial deafferentation from various causes, such as acoustic trauma or age-related hearing loss, produces a loss of inhibitory tone in the auditory system. Loss of central inhibition would be expected to significantly alter auditory processing (Willott and Lu, 1982, no. 76; Szczepaniak and Møller, 1996, no. 64; Suneja et al., 1998a, b, no. 60; Caspary et al., 1999, no. 15; Brozoski et al., 2002, no. 97) that in turn could lead to inappropriate neuroplastic changes eventually expressed as the sensation of tinnitus. Since γ -amino butyric acid (GABA) is a generally inhibitory neurotransmitter found in appreciable amounts at many levels of the central auditory pathway (Caspary et al., 1995, no. 221; Milbrandt, 1996, no. 219; Backoff, 1997, no. 215; Suneja et al.,

1998, no. 207; Bauer et al., 2000, no. 164), a corollary to the loss-of-inhibition and tinnitus hypothesis would be the down-regulation of GABA activity. If the linkage is causal, then restoring GABA function should reduce the perception of tinnitus.

Tinnitus has been compared to a variety of pain states including neuropathic pain, post-herpetic neuralgia, and phantom limb pain (see Chapters 1–4 and 18) (Tonndorf, 1987, no. 1432; Møller, 1997, no. 554). Features common to all these clinical syndromes include: onset after peripheral trauma, some degree of peripheral deafferentation, refractory management, central contribution to the chronic sensory experience, and the therapeutic action of centrally acting GABAergic drugs. The effects of gabapentin, 1-(aminomethyl)cyclohexanecarboxylic acid, on a variety of pain states has been extensively studied in clinical trials. Gabapentin is currently used to successfully treat migraine (Mathew et al., 2001, no. 62),

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post-herpetic and HIV-associated sensory neuralgia (Rice and Maton, 2001, no. 63; Hahn et al., 2004, no. 64), phantom limb (post-amputation) pain (Bone et al., 2002, no. 72), post-surgical pain (Rice and Maton, 2001, no. 63; Hahn et al., 2004, no. 64; Al-Mujadi et al., 2006, no. 71; Sihoe et al., 2006, no. 70), and tumor-related as well as non-tumor-related neuropathic pain (Serpell, 2002, no. 66; Caraceni et al., 2004, no. 69; Ross et al., 2005, no. 68; Wiffen et al., 2005, no. 67). Given the symptomatic and pathophysiological similarities between chronic pain and chronic tinnitus, GABAergic interventions for tinnitus are logical and studies have confirmed that they are beneficial in some patients. This chapter will review the current understanding of the mechanisms of action of gabapentin and vigabatrin, two GABAergic drugs recently shown to reduce tinnitus. Gabapentin was shown to be effective in some patients in two controlled clinical trials and to reduce the evidence of tinnitus in one animal study. Vigabatrin has recently been shown to effectively eliminate tinnitus in an animal study. Finally, the challenges of studying a complex disorder such as tinnitus will be discussed in the context of clinical trials and laboratory experiments.

Treatment of tinnitus with GABAergic drugs

Several GABA-enhancing drugs have been applied to the treatment of tinnitus. Benzodiazepines are GABA_A receptor modulators that have been shown to reduce the perceptual loudness of tinnitus in some patients (Johnson et al., 1993, no. 56; Huynh and Fields, 1995, no. 55). In contrast, the GABA_B modulator, baclofen, improved tinnitus in only 9% of the participants, not significantly different from the placebo response (3%) (Westerbergh et al., 1996, no. 15). Gabapentin was first reported to effectively reduce the loudness of tinnitus in a case report of new onset tinnitus of unknown etiology (Zapp, 2001, no. 61). Subsequent work in several uncontrolled trials demonstrated the efficacy of gabapentin, combined with the benzodiazepine clonazepam, for severe disabling tinnitus classified as central in origin (Shulman et al., 2000, no. 58; Shulman et al., 2002,

no. 57; Bahmad et al., 2006, no. 74). A prospective placebo-controlled single-blind study (Bauer and Brozoski, 2006) showed the effectiveness of gabapentin in treatment of tinnitus in some patients.

Mechanisms of action of gabapentin and vigabatrin

The mechanisms of action of gabapentin are not completely understood. Structurally, gabapentin is an amino acid and an analogue of GABA that crosses the blood-brain barrier (Satzinger, 1994, no. 54). However, gabapentin does not appear to bind to GABA receptors, nor does it modulate GABA receptor function. Gabapentin is not metabolically converted to GABA and it does not modulate GABA uptake or degradation (Taylor et al., 1998, no. 19; Lanneau et al., 2001, no. 10). There is some evidence, however, that gabapentin increases the synthesis of GABA from glutamate by enhancing the action of the synthetic enzyme glutamic acid decarboxylase (GAD) thereby increasing GABA concentration in the brain (Taylor et al., 1998, no. 73). Elevated GABA brain concentrations, evaluated with nuclear magnetic resonance (NMR) spectroscopy, have been reported in humans treated with gabapentin (Petroff, 1996, no. 17). Gabapentin also acts as a selective blocker of voltage-gated calcium channels containing the $\alpha 2\delta$ -1 subunit. This pre-synaptic mechanism of action, and the subsequent decrease in neurotransmitter release, may be primarily responsible for both the confirmed and anecdotal effects of the drug on a variety of clinical disorders, including tinnitus (Sills, 2006, no. 485).

In contrast to the lack of certainty about gabapentin's mechanism of action, the mechanism of vigabatrin's action is well-understood. Vigabatrin is a selective, irreversible inhibitor of GABA transaminase, the catabolic enzyme for GABA. Vigabatrin has antiepileptic activity and is used clinically for this indication. A number of animal (de Graaf et al., 2006) and human (Petroff et al., 1996) studies have demonstrated a dose-dependent elevation in central GABA levels after vigabatrin administration, including oral dosing in the drinking water of rats and monkeys (Bielicki et al., 2004). A recent animal study has shown vigabatrin

to be a potentially very effective tinnitus therapeutic (Brozoski et al., 2007, no. 442).

An animal model of tinnitus and the effect of GABAergic drugs

Animal models have facilitated basic research on the pathophysiology of tinnitus (Jastreboff et al., 1988; Jastreboff, 1995; Bauer et al., 1999b; Kaltenbach et al., 1999, 2004; Bauer et al., 2001; Brozoski et al., 2002; Lobarinas et al., 2004; Brozoski et al., 2005; Guitton et al., 2005; Heffner et al., 2005; Turner et al., 2006), and provide a method for screening compounds potentially useful in treating the disorder (see Chapters 12 and 13) (Bauer et al., 2001). There are several advantages in studying the efficacy of existing and novel drugs using animal models of tinnitus. Animal experiments permit control over salient variables such as genetic risk factors, acoustic exposure history, and causation. Clinical studies of tinnitus in humans are significantly challenged by these variables, in addition to the experimental confounds of placebo response and the affective or emotional components of tinnitus. It is also very challenging to find patients in which tinnitus can be definitively attributed to a known causal event. This is a significant problem because tinnitus is likely to be a disorder with a heterogeneous pathology, largely dependent on etiology. In contrast to human studies, animal experiments enable tinnitus etiology to be directly manipulated and well controlled.

The hypothesis that acoustic trauma-induced tinnitus results from a loss of inhibition via GABA mechanisms is supported by two laboratory animal studies using a behavioral conditioned suppression model of tinnitus. As previously noted, a corollary to the loss-of-inhibition-tinnitus hypothesis would be the prediction that elevation of GABA function in animals demonstrated to have tinnitus should reduce their tinnitus. This corollary was tested in two experiments investigating the effects of gabapentin and vigabatrin, respectively, on acoustic trauma induced tinnitus in rats using a conditioned suppression model (Bauer and Brozoski, 2001; Brozoski et al., 2007).

In one variation of the conditioned suppression model, rats are trained to discriminate between presentations of different auditory stimuli and to refrain from pressing a lever for a food reward when the auditory stimulus resembles their tinnitus. Tinnitus is induced by a single unilateral 60 min exposure to band-limited noise. The tinnitus-inducing stimulus is delivered monaurally to ensure that normal auditory thresholds are maintained in one ear, permitting the animal to detect and respond to sound presented in a free field. In this model, the induced tinnitus is tonal, typically in the 16–20 kHz range, and can be detected for many months over the life span of the individual (Bauer et al., 2001).

Acoustic brainstem evoked response (ABR) hearing thresholds are obtained before sound exposure, immediately after exposure, and typically before and after behavioral testing. The acoustic trauma parameters used in these experiments elevate ABR thresholds of exposed ears immediately after exposure without affecting thresholds of the unexposed ears (Fig. 1A). ABR thresholds of exposed ears months after exposure are minimally elevated above thresholds of the unexposed animals (Fig. 1B).

Rats are trained and psychophysically tested using an operant suppression procedure shown to detect tinnitus in animals (Bauer et al., 2001). Control animals not exposed to acoustic trauma are trained and tested in parallel with exposed animals. The objective of psychophysical training and testing is to derive discrimination functions reflecting sound perception. Briefly, animals are behaviorally trained to lever press for food in the presence of constant background sound, and to suppress lever-pressing during randomly introduced silent periods. Substitution of variable pitch and loudness tones for some of the silent periods enables derivation of psychophysical discrimination functions. The functions diverge at specific frequency–intensity values, indicating the presence of tinnitus in the acoustic trauma-exposed animals. Behavior is quantified in terms of a relative measure called a suppression ratio (R), which enables individual animal data to be compared and combined into group data by equally weighting the contribution of each animal

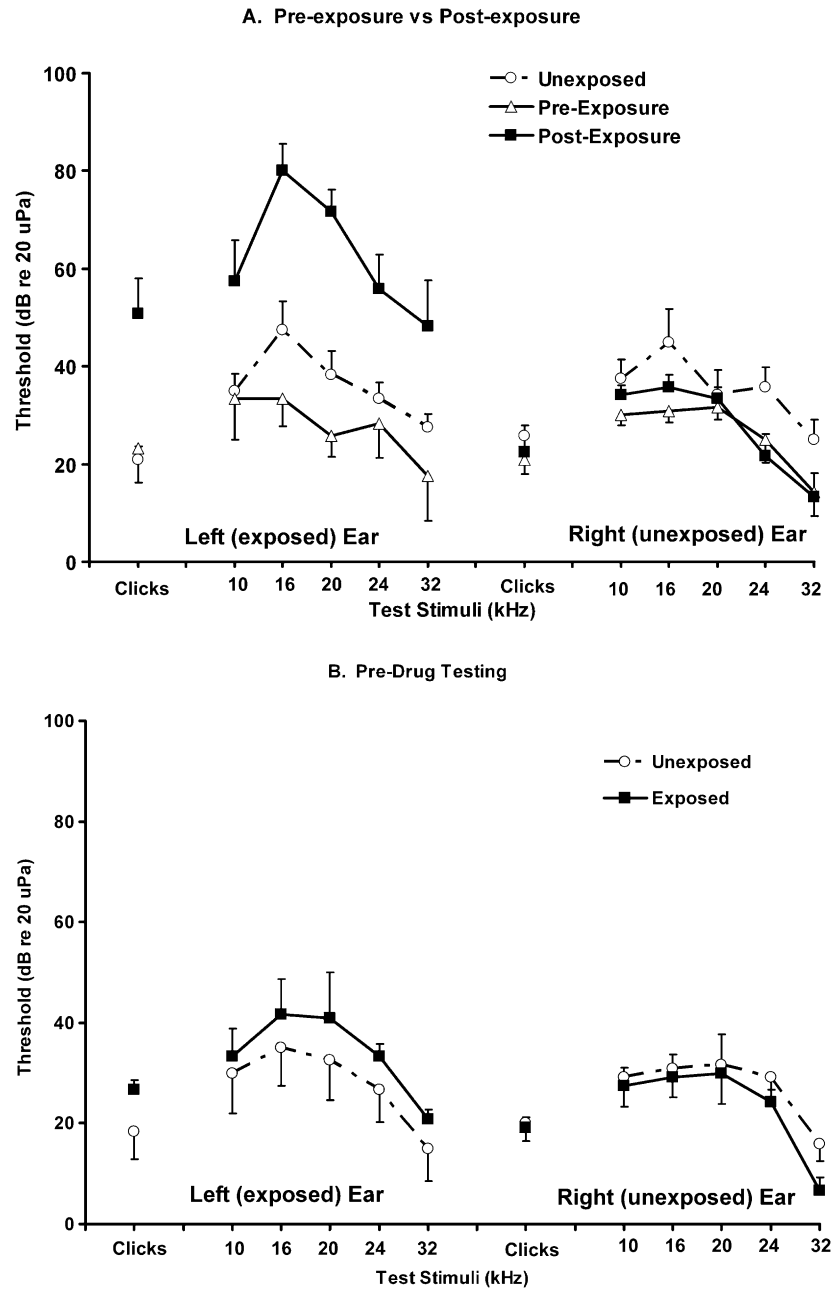


Fig. 1. Hearing thresholds, as indicated by ABR, obtained immediately before and after band-limited noise exposure (A), and at the conclusion of pre-drug training, approximately 4 months after exposure (B). The experimental animals were exposed once unilaterally (left ear) for 60 min while anesthetized, using a speaker driver attached to a cone-shaped speculum that fit tightly into the auditory canal. Peak stimulus intensity, centered at 16.13 kHz, was 120 dB (SPL), with an approximately linear decay to ambient levels at 8 and 28 kHz.

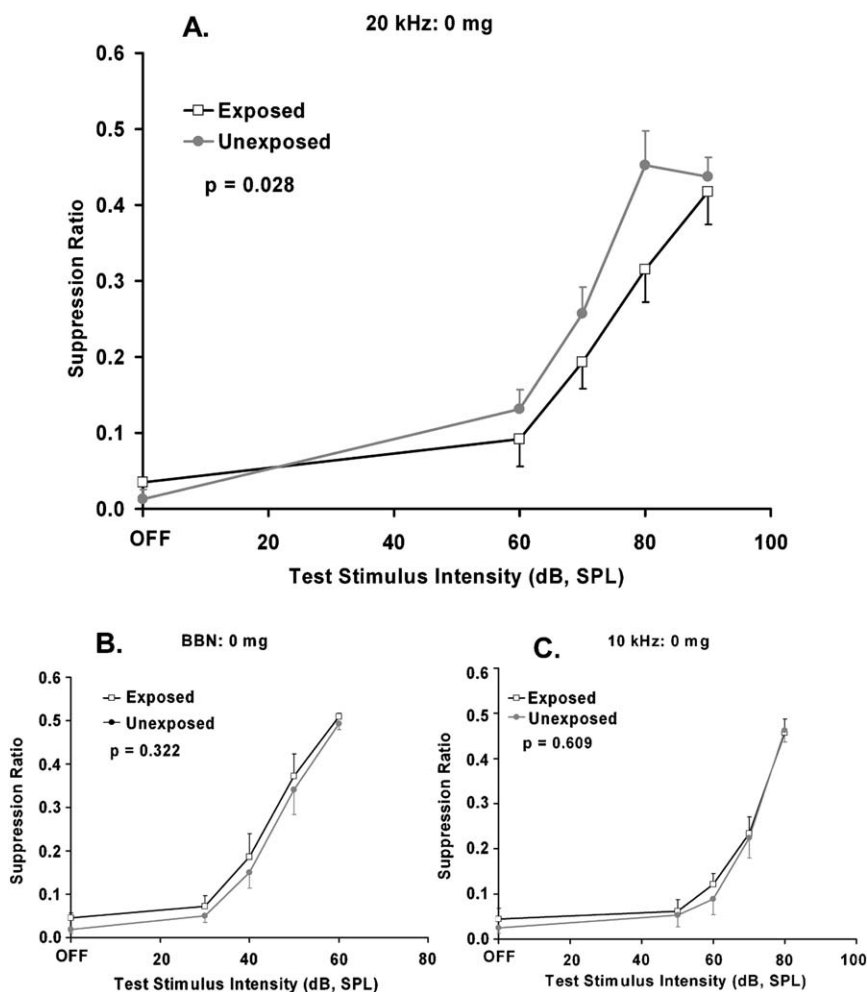


Fig. 2. Initial psychophysical performance, prior to any drug exposure. Downshift of the exposed group's 20 kHz discrimination function (A), with respect to the unexposed group's function, indicated the presence of tinnitus with characteristics resembling a 20 kHz tone. Discrimination of control stimuli (B and C) was not affected. Suppression ratio is a relative performance measure, 0 corresponding to no lever presses and 0.5 corresponding to a lever-press rate equivalent to baseline. Test stimulus presentations were 60 s in duration, randomly inserted into sessions of background sound (BBN, 60 dB, SPL; turned off during test stimulus presentations). $N = 6/\text{group}$.

irrespective of individual differences in lever-press rates.

Evidence of tinnitus is determined by the divergence of the exposed animals' 20 kHz discrimination function from the unexposed group's function: In this variation, tinnitus is indicated by a function downshift (i.e., enhanced suppression), and lack of tinnitus by the absence of a downshift, when tinnitus is induced before training and testing. Exposed animals demonstrated good

evidence of tinnitus with a significant downshift in their 20 kHz tone discrimination function when tested prior to drug treatment (Fig. 2A), relative to unexposed animals ($F_{1,40} = 5.199$, $p = 0.028$). As expected, there were no significant differences between exposed and control (unexposed) animals' performance when tested with non-critical stimuli (broad band noise (BBN): Fig. 2B, $F_{1,40} = 1.007$, $p = 0.322$; 10 kHz tones: Fig. 2C, $F_{1,40} = 0.266$, $p = 0.609$). The downshifted discrimination

function of the exposed animals indicated that the 20 kHz tones resembled their subjective sensation perceived during “speaker-off” or “silent” periods more closely than it did for unexposed animals (see behavioral training and testing, above). The assumption is that the presence of tinnitus affects perception of the acoustic environment, in other words, “silence” for exposed animals resembles a 20 kHz tone.

Gabapentin and acoustic trauma-induced tinnitus

Eight young adult male Long-Evans rats were exposed once unilaterally for 60 min to band-limited noise. The exposed animals were subsequently behaviorally trained and tested in parallel with eight unexposed control rats. The acoustic exposure resulted in robust suppression of lever-pressing during presentation of the 20 kHz test tones, compared with the matched psychophysical function of the control animals (Fig. 3A).

After baseline psychophysical performance was established, animals were divided into three treatment groups: acoustic exposure+drug, acoustic exposure+no drug, and no acoustic exposure+drug. Gabapentin was delivered as a solution in the animal's drinking water. Psychophysical testing was performed over a 10-day period on a low drug dose (1 mg/ml) and then repeated with a higher dose (2.5 mg/ml; average dose of 350 mg/kg/day). Gabapentin, at both the low and high dose levels, significantly reduced the shift of the psychophysical function of the exposed animals compared to the psychophysical function of exposed animals not on drug (Fig. 3B). Treatment with gabapentin had no effect on the behavior of the control animals in response to the 20 kHz test tone. These results showed that gabapentin reduced the evidence of acoustic trauma-induced tinnitus in rats without affecting hearing or general psychophysical performance.

Vigabatrin and acoustic trauma-induced tinnitus

The effect of the GABA agonist, vigabatrin, on rats with noise-induced tinnitus and controls without tinnitus was tested using the conditioned

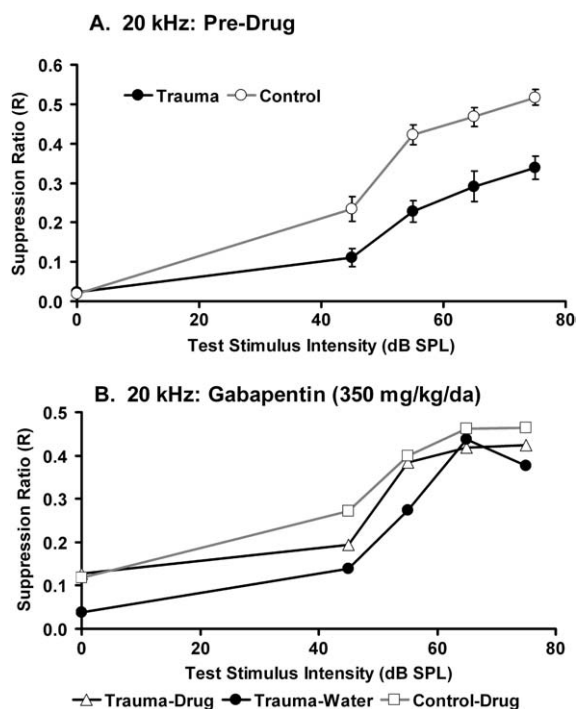


Fig. 3. Psychophysical functions for 20 kHz test tones obtained for trauma-exposed and unexposed animals prior to treatment with gabapentin (A). Psychophysical functions for the same animals are obtained after a 10-day treatment period of daily oral gabapentin (2.5 mg/ml) in their drinking water (B). The gabapentin reduces the downshift of the psychophysical discrimination function in the trauma-exposed animals, but has no effect on performance of the unexposed animals.

suppression model described above. The oral route of drug administration via drinking water and dose levels were derived from the study of Gleich et al. (2003), which documented the effect of vigabatrin on sound gap detection in gerbils. Vigabatrin (Sabril, lot 5485, Aventis Pharma Ltd., Kent, UK) powder was dissolved in tap water at either 0, 0.473, or 0.946 mg/ml, depending on the dose condition being tested. Average daily liquid consumption for all animals over the course of the experiment was 35.7 ml, resulting in an average drug dose level of 0, 30.3 (s.d. = 12.5), and 80.9 mg/kg/day (s.d. = 25.7), for successive test series. Drug testing was followed by a 7-week washout period, at the end of which a final test series was run without drug (0 mg/kg/day). The therapeutic benefit was greater than that obtained with gabapentin. Both the low and high doses of

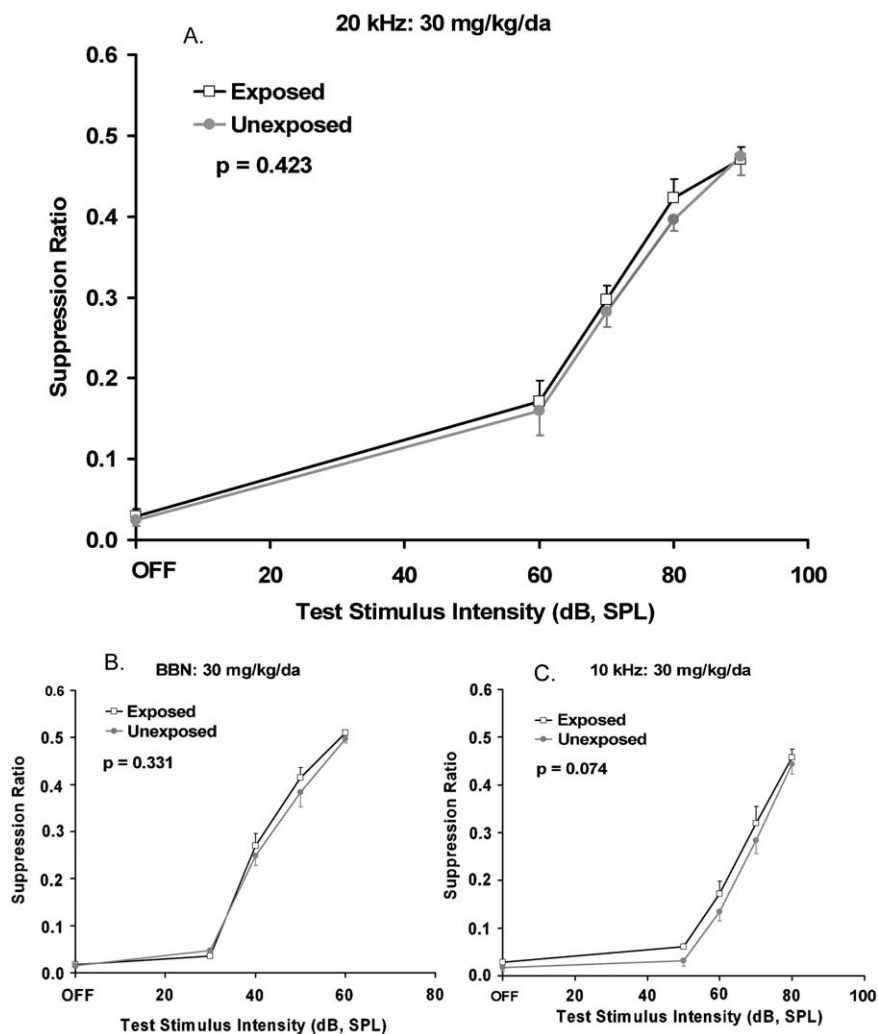


Fig. 4. Psychophysical functions obtained for trauma-exposed and unexposed animals treated with vigabatrin at 30.27 mg/kg/average daily dose. Animals and test parameters were as described in Fig. 2. There was no significant difference in discrimination performance between the exposed and unexposed animals.

vigabatrin eliminated the psychophysical evidence of tinnitus in the acoustic trauma exposed animals: Discrimination performance, for all acoustic stimuli tested was identical for both exposed and unexposed groups ((Fig. 4).

At the conclusion of the drug series, vigabatrin was removed from the animals' drinking water and the animals were maintained in their home cages for 7 weeks. At the end of this 7-week washout period psychophysical testing resumed with the animals off drug. Significant evidence of tinnitus

was again apparent in the exposed animals. The 20 kHz tone discrimination function of exposed animals was downshifted with respect to controls (Fig. 5A; $F_{1,40} = 4.286$, $p = 0.045$), while there was no difference between groups for BBN discrimination (Fig. 5B; $F_{1,40} = 0.002$, $p = 0.963$), or 10 kHz tone discrimination (Fig. 5C; $F_{1,40} = 1.496$, $p = 0.228$). These results clearly demonstrated the reversible effect of the drug on the psychophysical perception of tinnitus of the acoustic trauma-exposed animals.

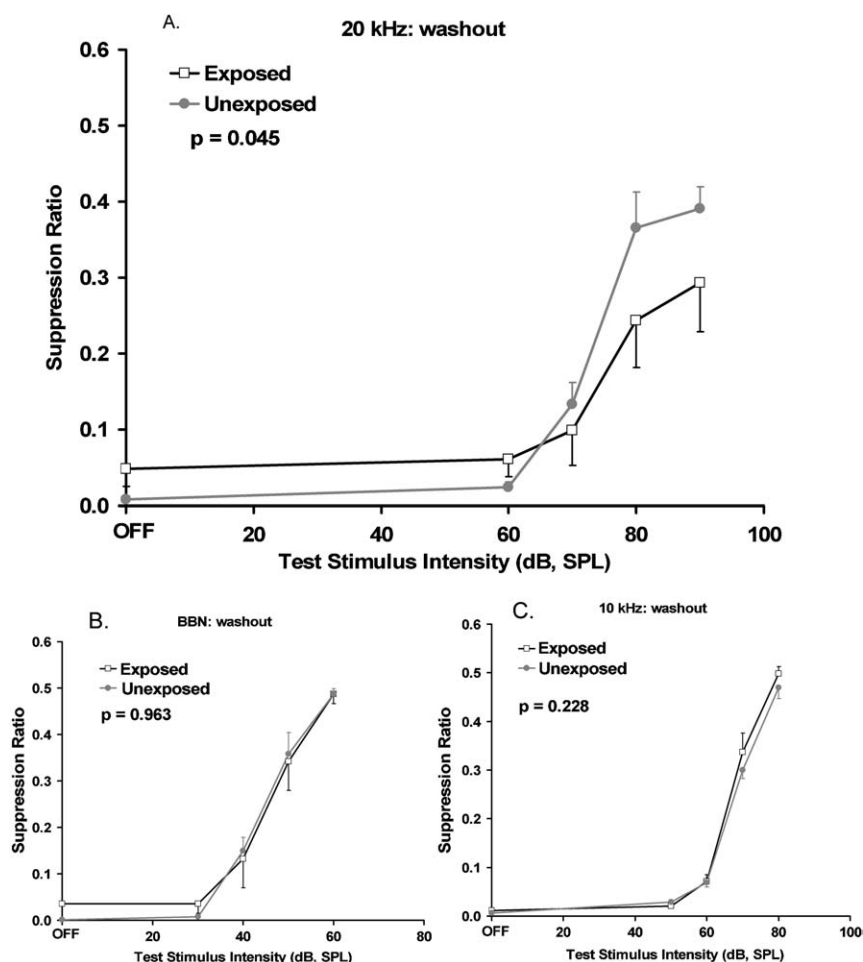


Fig. 5. Psychophysical functions for animals in Fig. 4, obtained after a 7-week washout period without vigabatrin. The significant difference between exposed and unexposed animals returned for 20 kHz tone discrimination.

Vigabatrin and central GABA levels

In order to confirm GABA elevation and examine its central distribution, two rats were given vigabatrin in their drinking water at 81 mg/kg/day, for 9 days. One of the animals was noise-exposed with evidence of tinnitus, the other was unexposed and without evidence of tinnitus. At the end of the 9-day drug period these animals, and two additional rats not on vigabatrin, underwent magnetic resonance imaging. GABA levels were estimated in the auditory brainstem and auditory forebrain, using (1)H magnetic resonance spectroscopy (MRS) guided by the brain images

(see Figs. 6B and C). A representative GABA brainstem spectrogram appears in Fig. 6A for a vigabatrin-treated animal. The results, reported as integrated GABA peak relative to the integrated *N*-acetyl aspartate reference peak, have been summarized in Table 1. Although the small *n* precluded inferential statistical analysis, the results were suggestive: Vigabatrin-treated animals, on average, had elevated brainstem GABA levels, and decreased forebrain GABA, compared to untreated controls. Brainstem areas included in the spectral analysis were the cochlear nuclei (dorsal and ventral), the posterior inferior colliculus, and the auditory nerve (Fig. 6B). Forebrain areas

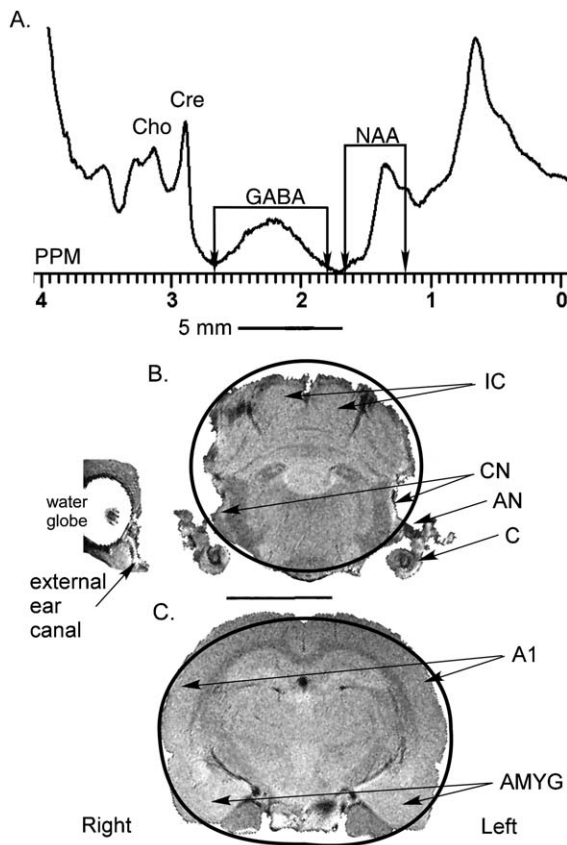


Fig. 6. (A) Brainstem GABA spectrum of a representative exposed animal treated for 9 days with vigabatrin at 81 mg/kg/day. GABA levels were determined as the integral of the GABA peak between 1.8 and 2.6 ppm, indicated by arrows, and reported relative to the *N*-acetyl aspartate peak (NAA) integrated between 1.2 and 1.6 ppm, indicated by arrows (also, see Table 1). (B) A representative brainstem slice from which brainstem spectra were determined (indicated by the encircled region). (C) A representative forebrain slice from which forebrain spectra were determined (indicated by the encircled region). The water-filled globe was located at the entrance to the right ear canal. Abbreviations: IC, inferior colliculus; CN, cochlear nucleus; AN, auditory nerve; C, cochlea; A1, primary auditory cortex; AMYG, amygdala. A 5 mm scale bar appears above each slice.

included in the spectral analysis included primary auditory cortex and amygdala (Fig. 6C). These tentative results support the hypothesis that central GABA is relevant to tinnitus pathophysiology and suggest that the therapeutic effect of vigabatrin may have been localized to more caudal rather than rostral regions of the auditory pathway.

Table 1. Relative central GABA concentration in the auditory forebrain and brainstem of rats ($n = 2$) treated with vigabatrin, 81 mg/kg/day, for 9 days prior to proton magnetic-resonance spectroscopy

GABA/NAA (integrated peaks)	Drug	No drug
Brainstem	3.24 (5.75; 0.73)	1.88 (2.42; 1.33)
Forebrain	0.98 (1.03; 0.93)	2.48 (1.04; 3.91)

Note: Control animals ($n = 2$) were not drug treated. Individual animals' data are shown parenthetically. GABA concentrations are reported as the integrated GABA peak (1.8–2.6 ppm) relative to the integrated *N*-acetyl aspartate peak (1.2–1.6 ppm) (Fig. 6A).

The results of both the gabapentin and vigabatrin studies are consistent with a specific hypothesis about the pathophysiology of chronic acoustic trauma-induced tinnitus: loss of inhibition in the central auditory pathway (Salvi et al., 1983; Brozoski et al., 2002; Diesch et al., 2004; Eggermont et al., 2004), and decreased GABA function are likely components of that decreased inhibition. From this hypothesis it was predicted that elevation of central GABA levels, using a drug such as vigabatrin, would effectively eliminate tinnitus. A secondary prediction was that the therapeutic focus of GABA agonists would be in the auditory brainstem, since brainstem areas have been widely implicated in the pathophysiology of tinnitus (Gerken, 1996; Backoff et al., 1997; Bauer et al., 2000; Davis et al., 2000; Kaltenbach et al., 2005). Vigabatrin, at moderate dose levels, completely eliminated the psychophysical evidence of tinnitus in rats. This therapeutic effect was specific, in that the auditory discrimination performance of control animals was unaffected by the drug (Brozoski et al., 2007), and it was reversible, disappearing after a washout period (Fig. 5).

Controlled trials of gabapentin and tinnitus

Two placebo-controlled human trials of the effect of gabapentin on tinnitus have been reported. The first (Bauer, 2006, no. 409) demonstrated a significant improvement in tinnitus annoyance for a group of participants with tinnitus related to acoustic trauma. In this study a subgroup of the

tinnitus-trauma participants also demonstrated a significant decrease in tinnitus loudness as indicated by stimulus loudness matching. The second study (Witsell, 2007, no. 488) did not detect any improvement in tinnitus handicap, but did report a significant improvement in subjective tinnitus annoyance when compared with placebo. The experimental designs and results of the two studies illustrate the significant challenges and pitfalls in studying a complex sensation such as tinnitus.

Witsell et al. (2007, no. 75) used a randomized, double-blind, placebo-controlled design to study the effect of gabapentin on tinnitus. The study was not stratified with respect to tinnitus etiology. The study sample size enabled it to detect a 50% reduction in tinnitus handicap at $\alpha < 0.05$. Fifty-three individuals were enrolled in the active treatment arm, and 26 individuals in the placebo arm (total $n = 79$). Fifty-five participants completed the study; 4 participants in the treatment arm and 10 participants in the placebo arm withdrew; 10 participants were lost to follow-up. Gabapentin was provided using an escalating dosage scale, with a maximum dose of 1800 mg daily for 2 weeks (weeks 3 and 4), followed by a 2 week taper. Participants in the placebo arm received capsules identical in appearance to the gabapentin capsules.

The primary outcome measure of the Witsell et al. (2007) study was the Tinnitus Handicap Inventory (THI), a validated questionnaire that examines self-perceived impact of tinnitus. The mean THI score on enrollment was 37.8 in the gabapentin group and 45.8 in the placebo group. Both the placebo and the gabapentin groups showed a significant decrease in THI score at the end of week 4 ($p < 0.004$), and did not significantly differ from one another. Although enrolled participants in each treatment arm were equivalent in tinnitus severity, they were significantly different at enrollment in Profile of Mood States scores (POMS) (gabapentin group 7.6 ± 30 ; placebo group 29.5 ± 42 ; $p, 0.026$). The POMS is a validated five-point ordinal rating scale that evaluates various mood dimensions. The enrollment scores on the POMS may have reflected an unintended group difference in tinnitus annoyance, resulting in a greater emotional burden from tinnitus in the placebo group. Despite this difference, it is notable

that 37.5% ($n = 18$) of participants in the gabapentin treatment arm reported a subjective improvement in tinnitus at the end of week 4, compared with 6.7% ($n = 1$) of participants in the placebo arm ($p < 0.026$).

The Bauer and Brozoski study (2006) examined the effect of gabapentin, across a broad dose range, on the loudness and annoyance of tinnitus in two populations of adults with moderate-to-severe chronic tinnitus. Individuals with historical and audiometric evidence of acoustic trauma, and individuals with no evidence of acoustic trauma were enrolled. This study was inspired and derived from the previously described gabapentin animal experiment (Bauer and Brozoski, 2001, no. 165). The results of this single-blind, placebo-controlled clinical trial of gabapentin demonstrated drug efficacy in reducing tinnitus annoyance in the trauma group and reducing tinnitus loudness in a subpopulation of the trauma participants (Bauer, 2006, no. 78).

Participants were prospectively recruited. Selection criteria included tinnitus of at least 1-year duration and at least moderate severity. Participants were categorized as either having trauma-related tinnitus ($n = 20$) or non-trauma-related tinnitus ($n = 19$) by history and audiometric profile. The study used a repeated measures design; all participants received gabapentin in an ascending-descending dose series extending over 20 weeks (peak dose 2400 mg/day); the dose series included a lead-in 2-week placebo period (capsules identical to gabapentin), and ended with a 3-week placebo washout period (capsules identical to gabapentin).

Participants were evaluated using an integrated computer-based assessment system. Prior to study entry and at the conclusion of each placebo and active drug period, participants were evaluated for subjective tinnitus severity using the Tinnitus Handicap Questionnaire and a tinnitus experience questionnaire (TEQ), mood disorder using the Beck Depression Inventory, hearing thresholds and tinnitus loudness using an objective psychophysical matching procedure. The matching procedure required participants to equate the loudness of their tinnitus to the loudness of 1 s tone (0.5, 1, 2, 4 kHz) and noise bursts (broad band) presented

in ascending–descending intensity series using the method of limits. Objective tinnitus loudness was indicated by the greatest sensation level match obtained in the entire test series, and was reported as dB hearing level.

A significant improvement in tinnitus annoyance ($p = 0.015$), as indicated by the TEQ, was obtained at 900 mg/day for the trauma group (Fig. 7A). A significant decrease in tinnitus loudness was also evident in upper half (i.e., the best responders) of the trauma group at 1800 and 2400 mg/day, but was not significant for the trauma group as a whole nor was it significant for the non-trauma group (Fig. 7B). A decrease in tinnitus loudness of at least 20 dB HL occurred in 6 of the 20 participants categorized as trauma-related tinnitus (mean 34, range 20.1–52.4). A similar degree of improvement was noted in only 3 of 19 participants categorized as non-trauma-related tinnitus (mean 32.8, range 20.4–44). A decrease in subjective (i.e., self-rated) tinnitus loudness of at least 20% (mean 30%) was observed in the same six trauma-related participants at one or more doses, compared to placebo. Four non-trauma-related participants had a similar decrease in subjective tinnitus loudness when on drug compared with placebo. Examples of the effect of treatment of an individual participant whose tinnitus was associated with trauma and improved on drug are shown in Fig. 8A and Fig. 8B shows similar data from a participant whose tinnitus was not related to trauma. While there were significant inter-individual differences in the degree of improvement in both subjective and objective measures of tinnitus, improvements were of larger magnitude and occurred more often in participants with trauma-related tinnitus. On the basis of this trial it may be concluded that gabapentin can be an effective therapeutic for a subpopulation of tinnitus patients, particularly those with associated acoustic trauma.

Challenges in studying tinnitus

Nearly all tinnitus treatments have been reported to produce some degree of improvement for some patients. The ubiquity of selective positive results

may be attributed, in part, to assessments that do not employ validated metrics or objective measures of tinnitus loudness. Studies that do not evaluate treatments using objective measures may be more likely to report placebo effects. The Witsell et al. (2007) study observed a strong placebo effect with a significant improvement in tinnitus handicap occurring in participants assigned to the placebo treatment arm. A placebo effect between 3 and 40% has been estimated to occur in clinical tinnitus studies (Al-Mujadi et al., 2006, no. 83). An effect of this magnitude has the potential to confound any clinical trial, particularly those focusing exclusively on subjective evaluations of tinnitus. Study designs that address placebo effects are especially important in studying a complex disorder that is primarily defined by its subjective features. The Bauer and Brozoski (2006) study addressed the problem of placebo effect in three ways: (a) participants were blinded with respect to treatment conditions; (b) a time-series design was used, in which every participant served as their own control and received all dose levels, including two 0 dose levels; and (c) objective psychoacoustic measures of tinnitus loudness, as well as multiple subjective measures of tinnitus, were used.

Including both subjective and objective measures of tinnitus is important for clinical trials evaluating tinnitus treatment. While tinnitus annoyance may be improved by the direct effect of decreasing tinnitus loudness, improvement may also occur because of indirect therapeutic effects on co-morbidities, such as sleep disorders, anxiety, depression and fatigue. In the second case, objective tinnitus loudness may not be altered but rather subjective improvement derives from alleviation of co-morbidities. Distinguishing direct from indirect therapeutic effects enables an improved understanding of mechanism of action and the underlying pathophysiology of tinnitus. Conjoint use of subjective and objective measurement also permits investigators to parse out the different components of tinnitus that consequently may be linked to therapeutic response.

Identifying characteristics of tinnitus patients that predict a positive therapeutic response remains a challenge. Different events that cause tinnitus may involve different cellular or neural

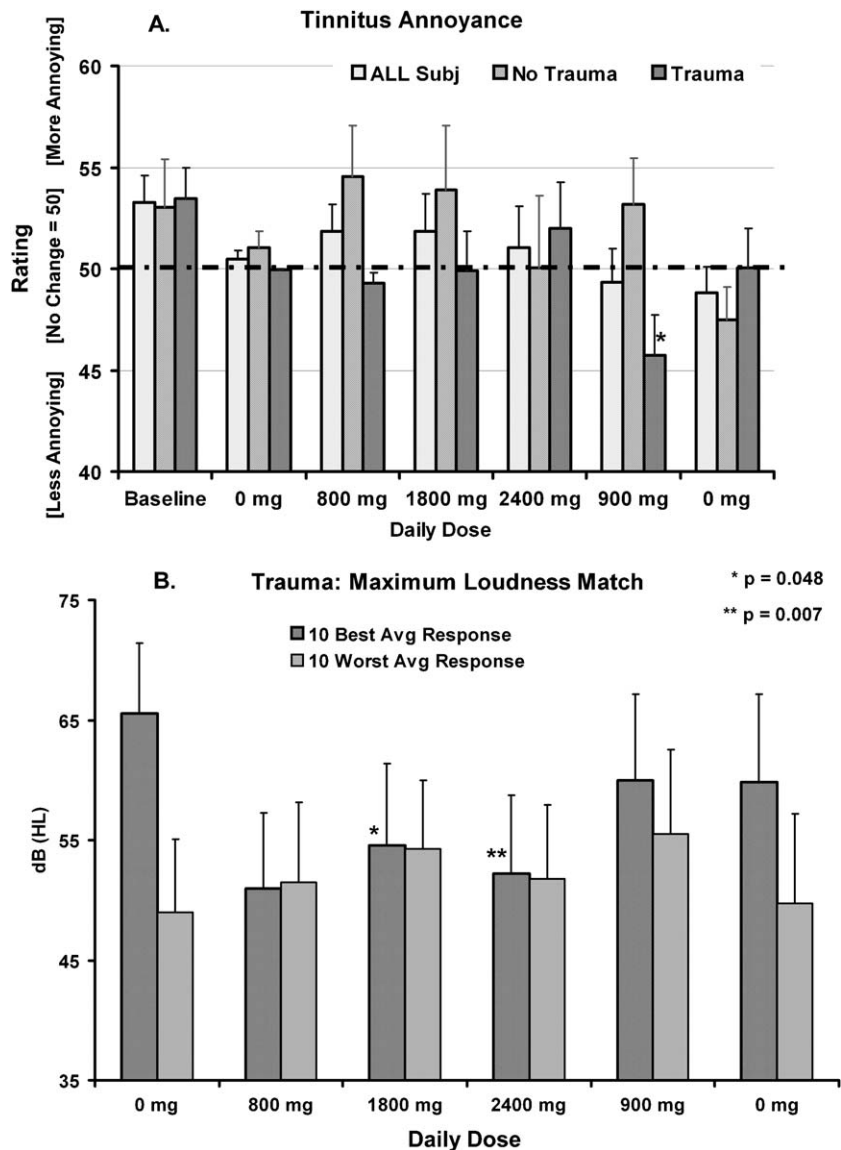


Fig. 7. Tinnitus annoyance for all participants (trauma and non-trauma) was measured at multiple gabapentin dose levels using the TEQ (A). There was a significant improvement in tinnitus annoyance for the trauma participants at the end of the trial during the 900 mg/day dose period. A conservative measure of improvement in tinnitus loudness is reflected in the matching tone with the largest absolute loudness in dB HL (maximum psychophysical loudness match). A subset of trauma participants experienced a significant decrease in tinnitus loudness during treatment with high dose gabapentin, and a washout of the objective improvement on low dose gabapentin and placebo (B).

mechanisms. It is likely that chronic tinnitus is a heterogeneous disorder for which there is no universally effective therapy. Clinical trials that fail to discriminate tinnitus subpopulations and identify them in their study designs, risk missing significant

treatment effects. A treatment effective in a subpopulation of patients, when tested in a heterogeneous population, can be washed out. The [Bauer and Brozoski \(2006\)](#) study addressed this issue by sampling from two tinnitus populations, identified

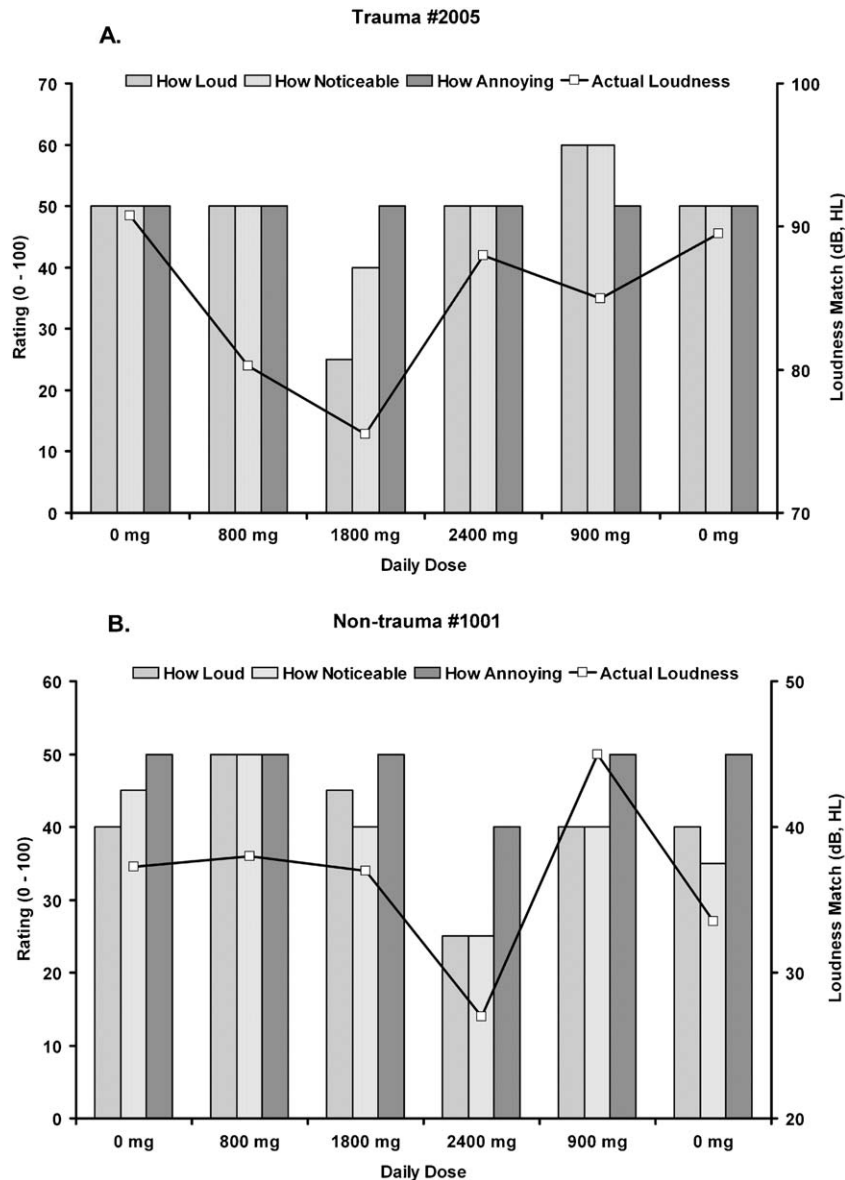


Fig. 8. Objective and subjective tinnitus measures for a trauma participant (A) and a non-trauma participant (B) illustrates the dose-dependent improvement in tinnitus loudness observed for some participants in the study. It is notable that, despite a significant reduction in both objective and subjective tinnitus loudness, the congruent tinnitus annoyance is not modulated in a corresponding fashion.

operationally on the basis of their audiograms, etiologically on the basis of history (i.e., trauma vs. no trauma reported) and theoretically on the basis of a likely physiological mechanism (i.e., loss of central inhibition vs. normal inhibition). Gabapentin was found to significantly decrease the

annoyance of tinnitus in the trauma group as a whole, and to significantly decrease the psychoacoustic loudness of tinnitus in a subgroup of trauma participants. While these results were promising, the data also suggest that more precise methods are necessary for identifying tinnitus

subpopulations that would benefit from targeted therapy.

Acknowledgments

The animal studies were supported by NIDCD RO1 DC4830-04. The clinical trial of gabapentin was funded by the Tinnitus Research Consortium. We are grateful to Luisa Ciobanu, Ph.D., Biomedical Imaging Center, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, for her expertise and assistance in obtaining the GABA spectra, and Kristin Myers, for her assistance in collection of animal data.

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CHAPTER 28

Lidocaine: neurobiological targets and effects on the auditory system

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Abstract: Lidocaine, a local anesthetic and anti-arrhythmic agent, is also known both as a tinnitus- and as a pain-suppressing drug. The sites of action in tinnitus suppression are in the cochlea as well as in the central auditory nervous system. In the present study, audiological and brain imaging studies in humans were used to identify the anatomical structure where lidocaine has its action on tinnitus. Molecular studies were used to elucidate the action of lidocaine on the cellular level. Various ion channels and receptors (e.g. voltage-gated Na^+ , K^+ and Ca^{2+} channels, glutamate, GABA, glycine and vanilloid receptors), found in the auditory system and possibly connected to tinnitus, are affected by lidocaine. Identification of molecular structures involved in expression of neuroplasticity in the auditory system in tinnitus and modeling the binding sites of local anesthetics could lead to the design of subtype-specific inhibitors that could provide new pharmacological targets for treatment.

Keywords: lidocaine; anesthetics, local; tinnitus; auditory system; hearing; ion channels; receptors; neurons

Introduction

Many different drugs have been tried for treatment of tinnitus, but with little success (e.g. Murai et al., 1992; Dobie, 1999; Simpson and Davies, 1999). Given the fact that tinnitus has many forms, it seems unlikely that a single theory or mechanism can explain the pathophysiology of tinnitus in every case (Møller, 2000). Tinnitus is a symptom, the origin of which varies, and a single drug is therefore unlikely to be effective in suppressing every kind of tinnitus. Intravenous administration of lidocaine reduces tinnitus in 40–80% of the patients (Murai et al., 1992) and therefore understanding the mechanisms of action of lidocaine on tinnitus may help elucidate the mechanisms of

tinnitus generation, but also lead to new pharmacological strategies in the treatment of tinnitus.

General use and clinical properties of lidocaine

Lidocaine (formerly known as lignocaine) is currently the most widespread local anesthetic in the world and is also used as an anti-arrhythmic agent (Tetzlaff, 1999; Baguley et al., 2005). Beginning with the accidental discovery of the tinnitus suppressing effect of the local anesthetic procaine (Bárány, 1935), intravenous administration of local anesthetics, such as that of the later synthesized lidocaine, started to play a role in the treatment of tinnitus (Murai et al., 1992) (see also Chapters 22 and 23). Assuming that the anatomical location of the action of lidocaine for tinnitus suppression is the cochlea, some investigators administered

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lidocaine in the intratympanic space to avoid systemic toxicity (e.g. Laurikainen et al., 1996; Dodson and Sismanis, 2004), another administered lidocaine by intradermal injection (Savastano, 2004). Lidocaine can partly suppress vertigo such as in Menière's disease when administered intravenously (Gejrot, 1976) or by intratympanic administration (Fradis et al., 1985; Itoh and Sakata, 1991); but lidocaine has little effect on motion sickness (Pykko et al., 1985).

Lidocaine has also been used to treat symptoms such as allodynia and hyperalgesia (e.g. Attal et al., 2000; Finnerup et al., 2005) that often occur as a component of neuropathic pain. Lidocaine can have both proconvulsant and anticonvulsant properties (Bernhard et al., 1955; Modica et al., 1990). Local anesthetics such as lidocaine also have antithrombotic (e.g. Cooke et al., 1977) and anti-inflammatory (Hollmann and Durieux, 2000) effects.

Side effects can include cardiac arrhythmia and central nervous system (CNS) excitation or depression, like drowsiness, dizziness and mild confusion, and occasionally hearing disturbances. Higher concentrations can produce CNS toxicity causing sedation or restlessness, tremulousness and convulsions (Steen and Michenfelder, 1979; Murai et al., 1992).

Because of poor biological availability after ingestion, lidocaine is not effective when taken orally. Attempts to develop analogs of lidocaine that can be administered orally have not been successful. Tocainide was developed as an anti-arrhythmic drug and tried for tinnitus with little success (Dobie, 1999). The drug is no longer available in the US because of severe side effects.

Chemical and pharmacokinetic aspects of lidocaine

Lidocaine is an amide-type local anesthetic with an aromatic lipophilic part, linked to a hydrophilic amine group by an intermediate chain. This structure of lidocaine and properties like its low molecular weight (234.33) and physiologic pK_a (7.86) allow it to pass quite easily through biological membranes like the round window membrane or

through the blood-brain barrier. Consequently, following application of lidocaine on the round window, diffusion into the cochlea leads to a rapid decrease of the cochlear microphonics (CM) and cochlear action potentials (CAPs) (Laurikainen et al., 1992). The uptake of lidocaine in rat brain corresponds to a brain-to-plasma partition coefficient (K_p value) of 2.2 under different plasma concentrations (1–15 μM) (Nakazono et al., 1991). No change of CAP and CM was reported after systemic administration of lidocaine or infusion in the anterior inferior cerebellar artery, indicating that systemically administered lidocaine may not pass the blood-cochlear (-labyrinth) barrier (Laurikainen et al., 1992). After intravenous administration in young pigmented rats accumulation of ^{14}C -lidocaine was found in the modiolus of the cochlea, but almost none in the stria vascularis (Englesson et al., 1976). While Laurikainen et al. (1992, 1997) used these results to support their suggestion that lidocaine may not pass the blood-labyrinth barrier and therefore may not enter the membranous labyrinth, Englesson et al. (1976) suggested that intravenous lidocaine has an effect on the inner ear and started clinical investigation on the effect of intravenous lidocaine in patients with tinnitus (for further information see also Sections "Cochlear site of action" and "Comments on other local anesthetics").

It is not clear to what extent lidocaine itself or its metabolites are responsible for the therapeutic qualities and side effects. In the liver, mixed-function oxidases metabolize lidocaine by dealkylation to monoethylglycine and xylide. These metabolites partly retain anti-arrhythmic activity and significant local anesthetic and toxic properties (Parnes et al., 1988). The possibility that the effect of lidocaine on the CNS is also mediated by the metabolites was supported by the observation that it takes more than 60 min to produce its maximum effect on the auditory brainstem response (ABR) (Javel et al., 1982; Parnes et al., 1988). The metabolization in the liver leads to a small oral bioavailability of ~30% and a half-life in systemic circulation of 90–100 min (Boyes et al., 1971; Burm et al., 1988), whereas $T_{1/2}$ for lidocaine in the cerebro-spinal fluid is considerably longer (Laurikainen et al., 1983).

Therapeutic studies and clinical concentrations in relation to molecular targets of lidocaine

While lidocaine is generally known as a sodium channel blocker, its effect on ion channels is more complex and it is unknown which structures, such as ion channels, are most relevant in explaining the action of lidocaine on tinnitus. The choice of a criterion for judging the relevance could be that a relevant structure should be most sensitive to lidocaine at the concentrations used clinically to suppress tinnitus or at least be significantly perturbed by them, similar to what is used in evaluating the effect of general anesthetics (Franks and Lieb, 1998). Thus, a minor effect of lidocaine at clinical concentrations may suggest that a molecular structure in the auditory system does not constitute a relevant pharmacological target for lidocaine. However, it should be noted that a concentration–response curve at the cellular level does not need to be identical with that of a neuronal network, modulated, e.g. multiplied or counteracted, on the way up the integrative structure of the CNS (Urban, 2002). Thus, modification of a very small fraction (less than 1–2%) of ion channels can have noticeable clinical consequences (Cannon et al., 1993). In order to assess the relevance of the effect of lidocaine at any level of the CNS, the structure of the underlying networks and how the individual components are linked must be known. Furthermore, pharmacologic sensitivity to lidocaine may change when experimental conditions are changed, as exemplarily illustrated by voltage-gated potassium (K_v) channels, if expressed in *Xenopus* oocytes, the pharmacological sensitivity of these channels is reduced for several substances in comparison to mammalian cell lines as expression system (Rolf et al., 2000). Also, the tetrameric K_v channels in the mammalian auditory system seem to be formed as heteromers by various combinations of K_v subunits instead of homomers, leading to different gating properties (Brew et al., 2003). Therefore, a different subunit composition in the neurons or the expression system chosen for studies could modulate the efficacy of lidocaine observed. It has been shown that various intracellular factors (Yi et al., 2001) and glycosylation (Watanabe et al., 2003) modulate the function of

these channels and could change their sensitivity to lidocaine (Trellakis et al., 2006).

Concentrations of lidocaine in a range from 1 to 2.5 mg/L are reported to suppress tinnitus in humans (Perucca and Jackson, 1985; den Hartigh et al., 1993). Side effects, including induction of tinnitus or hearing disturbances, may occur at concentrations between 2.5 mg/L (den Hartigh et al., 1993) and 4.7 mg/L (Chan et al., 1999) and persist to a plasma concentration of 0.5 mg/L (Strebel et al., 1993). Regarding plasma binding of lidocaine (60–70%) (Tucker et al., 1970; Routledge et al., 1980), suppression of tinnitus may occur at free arterial plasma concentrations from 1.75 to 3.5 μ mol/L whereas concentrations from 3.5 to 7 μ mol/L and above may induce tinnitus (Trellakis et al., 2006). There may be a considerable gradient between concentrations of lidocaine in the blood and in the brain. Studies of the tissue distribution of lidocaine in rats showed approximately five times higher concentrations in the brain than in the blood after systemic administration of lidocaine (Akerman et al., 1966).

Site of action of lidocaine in the suppression of tinnitus

Theories of tinnitus pathophysiology emphasize aberrant peripheral or central neural activity, and central dysfunction interacting with, and amplifying, a peripheral source of abnormal input (Bauer, 2004). For example, it has been assumed that an imbalance caused by insults to the peripheral structures may cause an imbalance in inhibitory and excitatory transmitter actions in the midbrain and the auditory cortex. The hyperexcitability caused by this imbalance may cause the perception of tinnitus (Eggermont, 2005) (see Chapters 1–3). Changes in spontaneous neural activity in auditory nerve fibers (ANFs), the dorsal cochlear nucleus (DCN), the inferior colliculus (IC) and the auditory cortex have been observed, following application of agents that are known to cause tinnitus (as loud noise, salicylate, quinine, aminoglycoside antibiotics and cisplatin) (Eggermont, 2005).

Thus, many hypotheses regarding the pathophysiology and the anatomical location of the

physiological abnormality that cause tinnitus have been presented. Many suggestions regarding the sites of action of lidocaine on tinnitus have been published including the cochlea, the auditory nerve and the central auditory pathways (Baguley et al., 2005). Below we will discuss the effects of lidocaine on central as well as on cochlear functions and we will review our understanding of the involvement of different molecular structures in the generation of tinnitus.

Brain imaging studies/central site of action

Functional brain imaging techniques, such as single photon emission-computed tomography (SPECT), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) can reveal changes of activity in the CNS by measuring the regional cerebral blood flow (rCBF) and are potential methods for the objective measurement of tinnitus (Mirz et al., 1999). Suppression of tinnitus induced by administration of lidocaine has been studied using different kinds of such imaging techniques (Mirz et al., 1999; Staffen et al., 1999; Andersson et al., 2000; Reyes et al., 2002). It has been shown in a PET study of 12 individuals with tinnitus that rCBF in the right middle frontal gyrus and the right middle temporal gyrus, furthermore in the right precuneus and the right paracentral lobule, changes after administration of lidocaine (rCBF during tinnitus minus rCBF after application of lidocaine) (Mirz et al., 1999). During further PET scans, subjects had their tinnitus sensation suppressed by masking sounds in the tinnitus-affected ear or ears without or in combination with lidocaine, resulting in different central activation. This study showed signs that administration of lidocaine and sounds applied to one or both tinnitus-affected ears suppress the generation of neural activity that is perceived as tinnitus at different anatomical locations and probably involving different mechanisms (Mirz et al., 1999). In a PET case study, Andersson et al. (2000) found signs of decrease in rCBF in the left parieto-temporal auditory cortex, including the primary and secondary auditory cortex with a focus in the parietal cortex (Brodmann

areas 47, 49 and 15) while tinnitus was suppressed by administration of lidocaine. A PET study of 13 individuals with tinnitus (Reyes et al., 2002) showed that the change in loudness of the tinnitus induced by administration of lidocaine was associated with a unilateral change in rCBF in the right temporal lobe (Brodmann areas 21, 22 and possibly 42) in the auditory association cortex, thus indicating that abnormalities in the neural activity in these structures may be involved in tinnitus. In the same study, probably non-tinnitus related effects of lidocaine were found in the basal ganglia, the left thalamus, and a region spanning the Rolandic fissure (central sulcus) on the right side. In an imaging study in which tinnitus loudness was modulated by orofacial maneuvers, change in rCBF was observed in the primary auditory cortex and auditory association cortex (Lockwood et al., 1998) indicating that these structures were involved in generating the tinnitus. In conclusion, all these brain-imaging results confirm a central action of lidocaine during suppression of tinnitus.

Another sign of central action of lidocaine is that abnormal spontaneous discharge of the auditory pathway evoked by administration of salicylate in an animal model of tinnitus temporarily diminished or is eliminated after intravenous administration of lidocaine [Evans et al., 1981 (cat); Martin et al., 1993 (cat); Manabe et al., 1997 (guinea-pig)]. Evans et al. (1981) observed that salicylate-induced increase of spontaneous discharge rate of single ANFs in cats was little affected by intravenous administration of lidocaine at a dose clinically used for treating tinnitus (1.5 mg/kg). Confirming results were reported by Martin et al. (1993) who used a dose of lidocaine four times higher in cats. Ruth et al. (1985) suggested that lidocaine may act more centrally than cochlear nerve fibers in the auditory system: the cochlear nucleus or superior olivary complex was a probable target since the V wave of the ABR, resulting from activity of IC neurons, was inhibited by intravenous lidocaine [the (vertex positive) peak V is generated by the termination of the lateral lemniscus in the central nucleus of the IC (Møller and Jannetta, 1983; Møller, 2006a)]. This does not preclude that lidocaine has an effect on neurons in the IC. Studies in monkeys (Velasco et al., 1982)

have supported involvement of the IC in the action of lidocaine in tinnitus inhibition in humans because they assumed that peak V of the ABR was generated in the IC. Similar studies in guinea pigs by [Manabe et al. \(1997\)](#) showed that salicylate-induced discharge in IC neurons was inhibited by intravenous lidocaine in an amount that corresponds to what is used clinically in patients with tinnitus (1 mg/kg). Because they observed IC neurons with small sensitivity to lidocaine and a short effect (<5 min) and some with high sensitivity and a longer duration of effect (>30 min) they speculated about different sensitivity to lidocaine as classification of two groups of IC neurons. Evidence that intravenous administration of lidocaine acts on the CNS is further supported by the finding that it also has a statistically significant inhibitory effect on tinnitus in patients after trans-labyrinthine removal of vestibular schwannoma ([Baguley et al., 2005](#)). This observation does not exclude that lidocaine may also have a cochlear mode of action in patients with an intact auditory nerve.

Cochlear site of action

After intravenous administration of labeled (^{14}C)lidocaine in pigmented rats, some accumulation was found in the modiolus, but almost none in the stria vascularis ([Englesson et al., 1976](#)). In opposite to [Laurikainen et al. \(1992, 1997\)](#) the authors interpreted these results as argument for an effect of intravenous lidocaine in the inner ear ([Englesson et al., 1976](#); [Lyttkens et al., 1979](#)). QX-572, a quaternary ammonium derivate of lidocaine, which does not readily penetrate the blood-brain barrier ([Rydén, 1974](#)), was compared with lidocaine by experimental and clinical investigation ([Lyttkens et al., 1984](#)). While labeled lidocaine showed a strong uptake in the brain of pigmented rats already 5 min after a single intraperitoneal injection of the drug ([Lyttkens et al., 1979](#)), no uptake of intraperitoneal injected ^3H -QX-572 was seen in the brain. There was an accumulation of the labeled QX-572 on the melanin of the inner ear. Furthermore, six of the nine patients with severe tinnitus who responded to intravenously

administered lidocaine also responded to QX-572. Therefore, the authors concluded that the effect on tinnitus is mediated by the same mechanism for both substances. Thus, since QX-572 does not penetrate into the brain, they postulated that the site of action is peripheral for both QX-572 and lidocaine.

Because tetrodotoxin, a specific blocker of sodium channels, did not affect CM, [Konishi and Kelsey \(1968\)](#) assumed that the ester type local anesthetic procaine has its effect by influencing calcium metabolism in the organ of Corti. Tetracaine, an ester type local anesthetic which interferes with calcium movement in muscle and non-muscle cells, inhibited the slow movements of isolated outer hair cells (OHCs) ([Slepecky et al., 1988](#)).

Lidocaine inhibits K^+ channel-induced isosmotic efflux and cell shrinking in isolated vestibular dark cells ([Wangemann et al., 1992](#)), and it might inhibit Ca^{2+} , Mg^{2+} ATPase and active $\text{Ca}^{2+}/\text{Na}^+$ exchange in plasma membranes and synaptosomes in certain areas of the brain tissue ([Gandhi and Ross, 1988](#); [Garcia-Martin et al., 1990](#); [Laurikainen et al., 1992](#)). The most likely mechanism of action of lidocaine on OHCs is its effect on K^+ channels and/or active $\text{Ca}^{2+}/\text{Na}^+$ exchange, alternatively on Ca^{2+} , Mg^{2+} ATPase or traditional Na^+ channels ([Laurikainen et al., 1992](#)). [Laurikainen et al. \(1992\)](#) showed that administration of lidocaine through the round window gave a dose-dependent reduction in the CM and the compound action potential. These investigators further found that systemic application of lidocaine did not affect the cochlear potentials, thus assuming that lidocaine does not pass the blood-cochlear barrier. Later, [Laurikainen et al. \(1997\)](#) showed that lidocaine in isolated OHCs decreased whole cell current in a concentration-dependent manner with a high (7 mM) half-maximal inhibitory concentration (IC_{50}). The greater part of this whole cell current is carried by K^+ through large- (BK or maxi-K channels) and small-conductance (SK channels) Ca^{2+} -activated K^+ channels ([Santos-Sacchi and Dilger, 1988](#); [Housley and Ashmore, 1992](#)), but also voltage-dependent/ Ca^{2+} -independent types of K^+ channels ([Van Den Abbeele et al., 1999](#)).

Recently, other channels in OHCs such as transient receptor potential channels (TRPCs) (Raybould et al., 2007), KCNQ4 (a M-type K^+ channel) (Kharkovets et al., 2006) or class D L-type voltage-gated Ca^{2+} channels (Engel et al., 2006) were also studied under physiologic and hearing-impaired conditions. In vivo studies using the sodium channel blocker tetrodotoxin (Konishi and Kelsey, 1968) and studies of voltage-clamped OHCs (Santos-Sacchi and Dilger, 1988; Housley and Ashmore, 1992) suggest that no traditional Na^+ channels exist in mammalian OHCs (Laurikainen et al., 1997). Nevertheless, “physiologically silent” Na^+ channels have been found in OHCs (Witt et al., 1994) and voltage-gated sodium (Na_v) channel subtypes such as $Na_v1.2$ and $Na_v1.6$ exist in cells in the organ of Corti close to OHCs (Hossain et al., 2005).

Studies on the effect of intravenous administration of lidocaine on the function of OHCs in individuals with tinnitus had yielded controversial results. These studies made use of recordings of the otoacoustic emissions (OAEs), which are used clinically to assess the function of the OHCs (Kemp, 1978; Hotz et al., 1994). In a study of 30 individuals with tinnitus Haginomori et al. (1995) found that transient-evoked otoacoustic emissions (TEOAEs) changed after intravenous administration of lidocaine (1 mg/kg over 2 min) in 18 ears, either by an increase or a decrease in amplitude. Tinnitus was suppressed in 94% of these 18 ears but tinnitus was also suppressed in 42% of the 12 participants in whom the OAE was not affected by administration of lidocaine. The authors concluded that there is a relationship between the effect of lidocaine in tinnitus suppression and changes in CM caused by lidocaine, but were criticized because neither the extent nor the duration of the change or the test-retest reliability of the TEOAEs amplitude was given (Baguley et al., 2005). Another human study found no significant changes in spontaneous OAE and distortion product otoacoustic emission (DPOAE) after intravenously administered lidocaine (1.5 mg/kg over 30 min in 30 patients with tinnitus) (Kalcioğlu et al., 2005).

Intratympanic injection of lidocaine (40 mg in 1 ml of saline, six patients with tinnitus) caused a 2–10 dB reduction in the TEOAE level at 1–3 kHz

frequencies with maximal reduction 30 min after injection (Laurikainen et al., 1996). These lidocaine injections did not change latencies or amplitudes of any component of the ABR in any of the patients, suggesting a specific effect on the organ of Corti, without significantly affecting the auditory nerve or central auditory pathways.

Because OAEs are affected by fluid in the middle ear (Ueda et al., 1998), it is difficult to evaluate the effect of lidocaine on the OHCs by OAEs after intratympanic administration (Maruyama et al., 2001). The OHCs have a mechanical function by affecting the vibration of the basilar membrane (Møller, 2006a). Therefore, changes in the function of the OHC are reflected in the vibration of the basilar membrane. Maruyama et al. (2001) measured the basilar membrane vibration in order to evaluate the effect of lidocaine administered directly into the scala tympani of guinea pigs. Both the velocity of basilar membrane vibration and the CAP amplitude decreased significantly, with a maximal decrease of 4 and 40 dB, respectively. These effects were not observed after intravenous injection of lidocaine (1.5 mg/kg). The authors concluded that the large decrease in the amplitude of the CAP could not be explained by the decrease in the vibration velocity of the basilar membrane and that lidocaine had an effect directly on cochlear nerve fibers, and that the reduction in the CAP amplitude is mainly due to a blockade of afferent fibers terminating on the inner hair cells. Furthermore, lidocaine might alter the compliance of OHCs by acting on contractile structures such as actin, resulting in the suppression of basilar membrane vibration.

In other animal studies, where procaine was applied into the guinea pig cochlea (Konishi and Kelsey, 1968) and lidocaine was administered intratympanically in cats (Hughes and Yagi, 1975) or in guinea pigs and rats (Laurikainen et al., 1992), CM and CAP were decreased, while the endocochlear potential remained stable or slightly increased. The observed effects on both the CM and CAP, especially the time course of CAP/CM changes and the degree of the CAP decrease at the higher frequencies, could indicate that these effects are specific pharmacologic mechanisms and actions of lidocaine on the inner ear by a primary effect on the basal turn hair cells (Laurikainen et al., 1992).

The effect of intravenous injection of lidocaine on hearing thresholds was studied in 10 healthy humans by [Shiomi et al. \(1997\)](#). Because the blockage rate of sodium channels by lidocaine is proportional to the number of open channels (use-dependent block, see next section), they hypothesized that, if lidocaine blocks the auditory tract by acting as a sodium channel blocker, the blocking effect was likely to be stronger for a continuous tone than for an intermittent one. Furthermore, in light of the study by [Laurikainen et al. \(1992\)](#), they expected to have a frequency-dependent effect of lidocaine on the hearing threshold. In most cases, increases, but also decreases in the threshold were observed. The higher the frequency, the more often the threshold was increased by lidocaine injection as a frequency-dependent effect. Continuous and intermittent tones resulted in no significant differences in the threshold change. The authors suggested that lidocaine may act more on the organ of Corti than on higher auditory tract neurons, but did not comment on the fact that this contradicts a blood-labyrinthine barrier for intravenous administered lidocaine as suggested by [Laurikainen et al. \(1992\)](#).

In studies in cats [Javel et al. \(1982\)](#) found that the latencies of the peaks in the ABRs increased during systemic infusion of lidocaine and that the changes in neural conduction time increased throughout the brainstem. They concluded that the observed changes supported the hypothesis that lidocaine increased both axonal and synaptic conduction times. Prolongations of both the absolute latency and the interpeak latencies of the ABR are reported to occur in some patients during and after intravenous infusion of lidocaine in individuals with tinnitus ([Ruth et al., 1985](#); [Lenarz, 1986](#); [Ueda et al., 1993](#)), supporting the results of other studies showing that the sites of action for lidocaine are both the auditory nerve and the brainstem.

Effect of lidocaine on ion channels and receptors

Voltage-gated sodium channels

Lidocaine as a local anesthetic has its effect in peripheral nerves by blocking Na_v (-dependent)

channels ([Butterworth and Strichartz, 1990](#); [Fozzard et al., 2005](#)). Na_v channels are essential in regulating neuronal excitability and in the generation and propagation of action potentials ([Hille, 2001](#)). They consist of a pore forming α subunit, associated with auxiliary β subunits (β_1 – β_4 in the adult CNS) modulating the level of expression and gating of these channels ([Isom, 2001](#); [Catterall et al., 2005a](#)). At least nine mammalian sodium channel isoforms ($\text{Na}_v1.1$ – $\text{Na}_v1.9$) have been characterized and functionally expressed, and other closely related proteins have been cloned from humans, but have not yet been functionally expressed (Na_v). $\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$ and $\text{Na}_v1.7$ are phylogenetically the most closely related group and highly tetrodotoxin-sensitive, $\text{Na}_v1.5$, $\text{Na}_v1.8$ and $\text{Na}_v1.9$ are also closely related, tetrodotoxin-resistant to varying degrees and highly expressed in heart and dorsal root ganglion neurons ([Catterall et al., 2005a](#)).

$\text{Na}_v1.1$, $\text{Na}_v1.2$, $\text{Na}_v1.3$, $\text{Na}_v1.5$ and $\text{Na}_v1.6$ are expressed in the adult brain ([Catterall et al., 2005a](#)), distinct Na_v channels such as $\text{Na}_v1.2$ and $\text{Na}_v1.6$ are distributed in multiple sites along the cochlear ganglion cells and nerve fibers, including the afferent endings, ganglionic initial segments and nodes of Ranvier ([Hossain et al., 2005](#)).

The existence of an enhanced subthreshold resonance in the ANFs dendrites that is caused by the activation of Na_v channels ([McMahon and Patuzzi, 2002](#)) may have relevance for the generation of tinnitus, because it may increase the probability of doublet-spike firing, as was observed following noise trauma in cat ANFs ([Liberman and Kiang, 1978](#); [Eggermont, 2005](#)). Therefore, these Na_v channels might be essential targets mediating the tinnitus suppressing effect of lidocaine. As orally active sodium channel antagonists have no effect on tinnitus, the mode of action of lidocaine on tinnitus might differ from the orthodox mode of action in sodium channel blockage, suggesting that other neurotransmission systems may be involved. Alternatively, an area of the auditory system that underwent plastic change or reorganization because of a peripheral change or a dysfunction (e.g. [Dietrich et al., 2001](#)) might synthesize certain Na_v channels, possibly having a

particular and selective affinity with lidocaine (Davies, 2001; Baguley et al., 2005). Both chronic tinnitus and chronic pain show similarities such as being related to expression of neural plasticity in the CNS (Møller, 2000) (see Chapter 3), possible involvement of Na_v channels (Max and Hagen, 2000) and suppression by lidocaine (Cahana et al., 2004) (see Section “Vanilloid receptor/pain”).

When hyperpolarized for long periods, Na_v channels exhibit a low affinity ($> 1 \text{ mM}$) for lidocaine. In contrast, high-affinity ($10\text{--}100 \mu\text{M}$) block is seen with repetitive depolarization, a phenomenon known as use-dependence (Courtney, 1975; Balser et al., 1996). Consistently, lidocaine has minor effects on quiescent cells, but overactive excitations that occur during pain (or tinnitus) may be suppressed (Fozzard et al., 2005). Lidocaine has different effects and potencies (15-times higher in brain channels) on brain and muscle sodium channels (Salazar et al., 1995). Voltage-clamp records of different Na_v channel isoforms, expressed in *Xenopus* oocytes, yielded different IC_{50} values for lidocaine in a range from 70 to $690 \mu\text{mol/L}$ ($\text{Na}_v1.2 < \text{Na}_v1.5, \text{Na}_v1.8 < \text{Na}_v1.4 < \text{Na}_v1.6, \text{Na}_v1.7, \text{Na}_v1.3$) and a pronounced prolongation of the time constant of the fast recovery process for the $\text{Na}_v1.3, \text{Na}_v1.5$ and $\text{Na}_v1.7$ isoforms (Hofer et al., 2006). A comparison of the effect of Na_v channel blockers used for pain treatment (lidocaine, mexiletine, benzocaine and ambroxol) on rat tetrodotoxin-resistant Na_v channels (representing mostly $\text{Na}_v1.8$) in sensory neurons and on heterologously expressed $\text{Na}_v1.2$ alpha subunits showed that all shifted steady-state inactivation curves to more negative values (Weiser, 2006). Lidocaine, mexiletine and benzocaine blocked $\text{Na}_v1.2$ more potently than resting tetrodotoxin-resistant Na_v channels in opposite to ambroxol.

It is possible to model the binding site of local anesthetics, localized to the middle of the sodium channel pore, and begin to correlate the differences in binding interaction between the several clinically useful drugs. Once the relationship between the binding region and channel gating is resolved, then the design of drugs to target-specific isoforms and specific gating states of Na channels will be possible (Fozzard et al., 2005).

GABA receptor/glycine receptor

The increase of spontaneous firing rates of neurons in the auditory system by agents and exposure to loud sounds that are known to induce tinnitus in humans has been attributed to reduced levels of central inhibition, probably γ -aminobutyric acid-(GABA)-ergic, in central auditory structures (e.g. Abbott et al., 1999; Bauer et al., 2000), leading to neural hyperactivity in the IC (Szczepaniak and Møller, 1996; Salvi et al., 2000; Eggermont, 2005).

Application of salicylate that is known to cause tinnitus in humans resulted in an upregulation of glutamic acid decarboxylase, the rate-limiting enzyme in the formation of GABA, and in a decrease in GABA_A receptor affinity in the IC of rats, which showed behavioral evidence for tinnitus (Bauer et al., 2000). An upregulation in the number of GABA_A receptors is observed in aging animals, probably to compensate for the loss of pre-synaptic GABA release (Ling et al., 2005) and perhaps promoting tinnitus (Eggermont, 2005) (see Chapter 2). Drugs with influence on the neurotransmitter GABA-like anticonvulsiva/tranquilizers, e.g. oxazepam, clonazepam (Lechtenberg and Shulman, 1984), alprazolam (Johnson et al., 1993) or gabapentin (Bauer and Brozoski, 2006) (see Chapter 27), and amino-oxyacetic acid (Reed et al., 1985), have been used in the treatment of tinnitus (Murai et al., 1992), as well as in the treatment or prevention of local anesthetic-induced convulsions (Modica et al., 1990).

Fusiform cells, major DCN output neurons, receive focused glycinergic inhibiting inputs from tonotopically aligned vertical cells, resulting in decreased tone-evoked activity (Casparly et al., 2005). Downregulation of bilateral glycine receptors in the DCN, the ventral cochlear nucleus and the lateral superior olive, and strengthening of glycinergic activity in the medial superior olive has been shown to occur after unilateral removal of one cochlea (Suneja et al., 1998; Eggermont, 2005). Also it has been suggested that markers for glycinergic neurotransmission in the DCN are lost with increasing age (Casparly et al., 2005).

In inhibitory receptors in the rat spinal cord, systemic administered lidocaine ($3\text{--}4 \text{ mg/kg}$) inhibited the excitatory responses to iontophoretic

glutamate in the same way as glycine. The effect was antagonized by the glycine antagonist strychnine. Biella and Sotgiu (1993) suggested that central inhibitory effects of lidocaine could be mediated by spinal strychnine-sensitive glycine receptors, activated by lidocaine itself or possibly by its glycine residue-bearing metabolites. Because tinnitus can be triggered or modulated by inputs from the sensorimotor systems (Møller et al., 1992; Cacace, 2003), a similar mechanism might underlie the observed suppression of some forms of tinnitus by administration of lidocaine.

Studies of the post-synaptic effects of application of lidocaine on excitatory and inhibitory amino acid-induced currents in rat hippocampal neurons showed that lidocaine (3 mM) decreased the glycine-induced Cl^- current more potently than the GABA-induced Cl^- current, whereas the agent had little effect on the excitatory glutamate response (Hara et al., 1995). A non-competitive inhibition was suggested for the effect on the glycine-induced Cl^- current. The inhibition of the glycine-induced Cl^- current seemed to be dependent on the charge of the local anesthetic used, as benzocaine, a neutral local anesthetic at physiological pH, was more effective than lidocaine and especially more effective than QX-314. QX-314 (*N*-(2,6-dimethylphenylcarbamoylmethyl)triethylammonium bromide; lidocaine *N*-ethyl bromide) is a permanently charged quaternary ammonium salt (QX) and derivative of lidocaine, which was particularly used to study the function of Na_v channels and the molecular pharmacology of local anesthetics related to these channels (e.g. Kimbrough and Gingrich, 2000).

The effects of local anesthetics on GABA-induced currents of receptors with different subunit combinations in *Xenopus* oocytes were examined by voltage-clamp technique (Sugimoto et al., 2000). Lidocaine led to an IC_{50} (mM) of 22 for subunit combination $\alpha 1\beta 2$, 12 for $\alpha 1\beta 2\gamma 2s$, and 46 for $\alpha 4\beta 2\gamma 2s$. A lack of pH dependence was observed for the GABA-induced current, which is opposite to what occurs in Na_v channels. The relative inhibitory potency was in the order of tetracaine > procaine > lidocaine > bupivacaine, thus ester-type local anesthetics were more potent than the amide-type ones. The results indicated that the

α and γ subunits of GABA_A receptors modulated the inhibitory effects of local anesthetics, and that local anesthetics can activate the $\beta 2$ subunit and may block the GABA_A receptor channel pore.

When synaptosomes or membranes, prepared from rat cerebral cortex, were used to compare the interactions of representative agents from each class of anesthetics with well-characterized radioligand binding assays (Lingamaneni and Hemmings, 2003), it was found that lidocaine and tetracaine only weakly inhibited ligand binding of GABA_A receptors at supratherapeutic concentrations ($\text{IC}_{50} > 4 \text{ mM}$), which is opposite to the action of intravenously administered or volatile anesthetics. Tetracaine antagonized isradipine, binding to L-type Ca^{2+} channels, more potently than lidocaine at high concentrations (IC_{50} 625 μM and 5630 μM , respectively). None of the drugs tested were potent antagonists to isradipine and to a ligand of K_{ATP} channels. Lidocaine and tetracaine selectively antagonized [^3H]batrachotoxinin A 20- α benzoate, binding to Na_v channels, with clinically effective concentrations (IC_{50} 128 μM and 1.4 μM , Hill coefficient (Hill, 1910) ~ 1 , respectively). In previous studies, lidocaine was shown to antagonize radioligand binding with similar IC_{50} values [311 μM (Postma and Catterall, 1984) or 240 μM (Creveling, et al., 1983) for Na_v channels, 3000 μM (Hirota and Lambert, 1996) or 14,800 μM (Kwon and Triggle, 1991) for L-type Ca^{2+} channels (Lingamaneni and Hemmings, 2003)].

GABA_B is a metabotropic receptor, built from two related seven-transmembrane domain receptor subunits and located on both pre- and post-synaptic terminals. Activation of the pre-synaptic GABA_B receptor regulates the release of many neurotransmitters, while activation of the post-synaptic GABA_B receptor produces long-lasting inhibitory currents, both may be involved in plasticity processes. A small change in the function of GABA_B receptors may be potentiated by the combination of the pre- and post-synaptic effect, may resulting in a shift of the normal excitatory and inhibitory balance (Li et al., 2003; Kornau, 2006). There is only little useful data about the effect of lidocaine and its derivatives on GABA_B receptors. While intracellular applied QX-314 blocks

voltage-dependent sodium currents at ~ 0.5 mM (e.g. Connors and Prince, 1982), high concentrations of QX-314 (5–15 mM) are needed to block GABA_B (mediated) currents (e.g. Otis et al., 1993; Perkins and Wong, 1995). Repetitive injection of very high, but subconvulsive doses of lidocaine (65 mg/kg) in rats lead to an increased and persisting seizure susceptibility to lidocaine over time (drug-kindled seizures). This behavior was accompanied by upregulated GABA_B receptor subunit expression in the hippocampus (Li et al., 2003). The authors suggested that those molecular changes could be a compensatory response to the functional loss of GABA interneurons caused by lidocaine blockade of the Na⁺ channel.

In summary, it seems that GABA and glycine receptors play a role in the excitatory side effects of lidocaine, e.g. convulsions at high clinical concentrations, but that these receptors are not involved in suppression of tinnitus by lidocaine.

Glutamate receptors

Glutamate receptors are the major excitatory neurotransmitter receptors of the CNS, including α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainite, delta, *N*-methyl-D-aspartate (NMDA) and metabotropic types. They are found widely distributed in the cochlear nuclei (Petrálie et al., 2000) and at all levels of the auditory system (Kaltenbach et al., 2005). NMDA and GABA receptors, especially, are active in the functional adaptation of neurons such as phenomenon of neuroplasticity (Cacace, 2003; Kaltenbach et al., 2005; Nitsche et al., 2005). NMDA receptors are involved in sprouting of afferent ANFs after cochlear damage (d'Aldin et al., 1997). Guitton et al. (2003) suggested that salicylate induces tinnitus through activation of cochlear NMDA receptors, followed by burst firing activity in ANFs.

In a study of the effect of lidocaine on NMDA receptors, where human NMDA receptors consisting of the essential subunit NR1 and the modulating subunit NR2A were recombinantly expressed in *Xenopus* oocytes, the responses to glutamate were reduced more than 60% after application of 10^{-7} M or greater lidocaine

(Hahnenkamp et al., 2006). The authors suggested that the inhibition of human NMDA receptors by local anesthetics is independent of their charge, that the site of action is intracellular, and that the mechanism of action is likely to be mediated indirectly by inhibition of protein kinase C. In contrast to these results, Nishizawa et al. (2002) could not find an inhibitory effect on NMDA-induced currents by clinically used concentrations of lidocaine in CA1 mouse pyramidal neurons. Hahnenkamp et al. (2006) suggested that the difference in results could have been caused by differences in the model or in the NMDA receptor subtypes or other choice of agonists, such as NMDA instead of physiological agonists of glutamate and glycine receptors.

Local anesthetics (bupivacaine, lidocaine, procaine and tetracaine) reversibly and concentration-dependently inhibited recombinant heteromeric mouse NMDA receptors, expressed in *Xenopus* oocytes. IC₅₀ for lidocaine was approximately 1170 μ M for the $\epsilon 1/\zeta 1$ receptor and approximately 1820 μ M for the $\epsilon 2/\zeta 1$ receptor (Sugimoto et al., 2003).

Low concentrations of lidocaine (40–60 μ M) had a selective action on nociceptive transmission in the rat spinal cord including a reduction of directly or synaptically driven NMDA and neurokinin receptor-mediated post-synaptic depolarizations, possibly acting on TTX-resistant sodium channels (Nagy and Woolf, 1996).

Voltage-gated potassium channels

Voltage-gated (-dependent) potassium (K_v) channels form the largest family among the group of human potassium channels. They show a great diversity and modification of function, e.g. because of forming heterotetramers, association and modulation by accessory proteins, and post-translational modification (Gutman et al., 2005).

K_v channels seem to play an important role not only in the cochlea (see above), but also in the processing of auditory information in auditory nuclei (e.g. Grigg et al., 2000) and in hearing disorders such as some forms of congenital deafness (Leao et al., 2004), presbycusis (von Hehn et al.,

2004) and aminoglycoside-associated ototoxicity (Liu and Kaczmarek, 2005). Mice carrying a deletion in the $K_v1.1$ encoding gene exhibited an extreme sensitivity to sound (Petersson et al., 2003). Expression of $K_v1.1$ and $K_v3.1$ channel subunits in the avian cochlear nucleus was temporarily down-regulated after cochlea removal (Lu et al., 2004). Various auditory neurons possess at least two forms of K^+ conductances that contribute to their firing pattern. A rapidly activating K^+ conductance with low threshold causes firing of only a single action potential instead of sustaining repetitive firing. A K^+ conductance with high threshold enables a rapid repolarization after action potentials necessary for high-frequency firing and is e.g. typical for the firing pattern of bushy cells in the ventral cochlear nucleus and also identified in IC neurons (Li et al., 2001; Brew et al., 2003). The low threshold activating K_v channel $K_v1.1$ and the high threshold activating K_v channel $K_v3.1$ likely contribute to these K^+ conductances in neurons in auditory nuclei (Trellakis et al., 2006).

Lidocaine (10 mmol/L) caused a more than half-maximal current inhibition of $K_v1.1$ channels expressed in *Xenopus* oocytes (Elliott et al., 1998). Lidocaine (100 μ mol/L) had only negligible effects on $K_v1.1$, $K_v1.2$ and $K_v1.4$ channels when studied in *Xenopus* oocytes (Rolf et al., 2000). Different sensitivities to the inhibitory action of lidocaine were observed in patch-clamp recordings on $K_v3.1$ channels, natively expressed in the neuron-like human neuroblastoma cell line SH-SY5Y, and $K_v1.1$ channels, expressed in human embryonic kidney (HEK293) cells (Trellakis et al., 2006). The IC_{50} for conductance block was 607 μ mol/L for $K_v3.1$ and 4550 μ mol/L for $K_v1.1$ channels. Conductance block was voltage-dependent for $K_v3.1$, but not for $K_v1.1$ channels. The midpoint of current activation of both channels was shifted to hyperpolarized potentials. In spite of the known limitations of in vitro experiments and the various modulating factors, the small effect at clinically used concentrations suggested that the physiologic roles of $K_v3.1$ and $K_v1.1$ channels in neurons in the auditory nervous system does not become impaired by application of lidocaine (Trellakis et al., 2006).

Vanilloid receptor/pain

The vanilloid receptor type 1 (VR1) also known as the transient receptor potential channel vanilloid 1 (TRPV1) is a ligand-gated non-selective cation channel, which is activated by capsaicin, lipoxygenase products, heat and acid, and related to the sensation of pain. VR1 was shown to be expressed by both spiral ganglion neurons (rat/guinea pig) and hair cells. Activation of VR1 may therefore contribute to hypersensitivity of ANFs in response to activation by hair cells under different pathologic conditions, such as e.g. tinnitus (Balaban et al., 2003). Activation of VR1 may at least play a role in cochlear homeostasis (Zheng et al., 2003). Furthermore, VR1 is commonly expressed in the dorsal root and trigeminal ganglion cells with possible effects on tinnitus (Eggermont, 2005). The lower brainstem, the cerebellum and the cochlear nuclei also contain cells with VR1-like immunoreactivity (Mezey et al., 2000). VR4 has been proposed to be an osmosensitive and mechanosensitive channel. It has been found in inner and OHCs as well as in spiral ganglion cells of the mouse (Shen et al., 2006).

Lidocaine and other local anesthetics inhibited capsaicin-increased intracellular Ca^{2+} in recombinant rat VR1, expressed in human embryonic kidney (HEK293) cells, in a concentration-dependent manner with a complete inhibition at 10 mM (Hirota et al., 2003). These investigators suggested that local anesthetics may act as VR1 receptor antagonists, but did not determine their exact site of action.

Chronic tinnitus and chronic pain show considerable similarities, including plastic changes in the CNS (Møller, 2006b), leading to hypersensitivity to sensory stimuli (Møller, 2000; Eggermont, 2005) (see Chapters 2 and 4). The antiallodynic and antihyperalgesic effects of intravenous lidocaine have been demonstrated both in animal models of neuropathic pain (Abdi et al., 1998) and in patients with different kinds of pain (e.g. Attal et al., 2000; Cahana et al., 2004; Finnerup et al., 2005).

Hains et al. (2003) demonstrated that $Na_v1.3$ is upregulated in dorsal horn sensory neurons in segments below a contusion spinal cord injury, contributing to hyperexcitability and hyperalgesia.

Therefore, abnormal sodium channels are one possible site of action of lidocaine in pain suppression (Finnerup et al., 2005). The fact that lidocaine at therapeutic concentrations affects hyperexcitable neurons without affecting normal nerve conduction Finnerup et al. (2005) emphasizes that lidocaine has its action on central nervous structures.

Voltage-gated calcium channels/calcium signaling

There are 10 members of the voltage-gated (or voltage-dependent) calcium channel family, mediating calcium influx in response to membrane depolarization and regulating many intracellular processes as well as neuronal excitability (Catterall et al., 2005b). The function of the hair cells depends on the Ca^{2+} signaling pathways. Furthermore, Ca^{2+} seems to play a role in the fast transduction process in hair cells (Kennedy et al., 2005) and is increased in hair cells by agents that are known to induce tinnitus (Fridberger et al., 1998). Administration of an L-type Ca^{2+} blocker (nimodipine) prevented quinine-induced signs of tinnitus in animals (Jastreboff et al., 1991).

All local anesthetics tested inhibited ATP-dependent Ca^{2+} uptake by the plasma membrane of synaptosomes from rat brain at concentrations close to those, which promoted an effective blockade of the action potential (Garcia-Martin et al. 1990). The IC_{50} values for inhibition of calcium uptake were 0.44 mM for lidocaine, 23 μM for dibucaine, 1.5 mM for procaine and 0.8 mM for tetracaine. The effects of local anesthetics such as lidocaine might result from a failure of synaptic transmission owing to a depletion of neurotransmitter-loaded vesicles (Manabe et al., 1997).

All local anesthetics concentration-dependently inhibited both evoked cytosolic Ca^{2+} transients with the potency order bupivacaine > ropivacaine > lidocaine \geq mepivacaine (Xu et al., 2003). The cytosolic Ca^{2+} was evoked by application of potassium chloride and carbachol in the neuron-like human neuroblastoma cell line SH-SY5Y. The evoked cytosolic Ca^{2+} transients were more sensitive to application of lidocaine without potassium chloride or carbachol prestimulation with IC_{50} values in a range

from 0.23 to 1.1 mM than with such stimulation. These investigators (Xu et al., 2003) suggested that different and overlapping sites of action of local anesthetics are involved in inhibiting evoked cytosolic Ca^{2+} transients, including voltage-gated Ca^{2+} and K^{+} , but not Na^{+} channels, as Na^{+} channel blockade did not alter Ca^{2+} transients with or without a local anesthetic.

When inhibition of voltage-gated Ca^{2+} channels in a rat pituitary clonal cell line by extracellularly applied lidocaine were compared with inhibition by nicardipine, a dihydropyridine Ca^{2+} channel antagonist (Xiong and Strichartz, 1998) it was found that the inhibition was greater at a holding potential of -60 mV (IC_{50} at 1.2 mM) than at -80 mV (IC_{50} at 2.6 mM) independent of the presence of nicardipine. The investigators suggested that lidocaine has a direct action on membrane Ca^{2+} channels, similar to the voltage-dependent action of dihydropyridine, but acting at a separate and independent site.

Other channels and receptors

Other channels and receptors than those discussed above may be targets of lidocaine in its action to suppress tinnitus. For example, inhibition of G protein-coupled receptor signaling by local anesthetics such as lidocaine has been found to be time dependent and reversible when studied in *Xenopus* oocytes (Hollmann et al., 2004). Lidocaine also inhibited muscarinic receptors of the m1 subtype, the most common subtype in the CNS with an IC_{50} (18 nM) (Hollmann et al., 2000), which was significantly less than needed for blocking sodium channels. Competitive inhibition in a binding assay showed contrary sensitivity to former results (Fairhurst et al., 1980). Evidence for cholinergic receptor upregulation was found in the DCN of rats in connection with sound-induced plasticity (Kaltenbach and Zhang, 2007).

Between 300 μM and 1 mM lidocaine partially displaced the specific binding of [^{125}I]cyanopindolol to β_1 -, but not to β_2 - and β_3 -adrenoceptors as shown in radioligand experiments in the Chinese hamster ovary (CHO) cloned human β_1 -, β_2 - and β_3 -adrenoceptors cells (Sakamoto et al., 2004).

Lidocaine (10, 100 and 1000 μM) tends to reduce basal adenosine 3',5'-cyclic monophosphate (cAMP) level on cells expressing β_1 -adrenoceptors.

Comments on other local anesthetics

In addition to lidocaine, other local anesthetics, especially procaine and tetracaine, have been used in clinical studies of their ability to suppress tinnitus, but with varying success (Murai et al., 1992; Dobie, 1999). Although tetracaine is the primary amine analog of lidocaine, but less lipophilic, it does not appear as effective (Murai et al., 1992). Because of the occurrence of prolonged (1-month) suppression of tinnitus after peripheral nerve block with lidocaine and bupivacaine in a single patient the investigator suggested further research with bupivacaine in tinnitus treatment (Weinmeister, 2000). The experience of prolonged binding of bupivacaine in the inner ear (Lyttkens et al., 1979) may support this idea, but there is still no adequate study for the treatment of tinnitus with racemic bupivacaine, the *S*-enantiomer levobupivacaine or related substances such as ropivacaine, and investigators have to pay attention to the cardiovascular toxicity of bupivacaine (Hollmann et al., 2001). QX-572, a quaternary ammonium derivative of lidocaine (such as QX-314) with corresponding effects to lidocaine (Rydén, 1974), suppressed tinnitus in six of nine patients with tinnitus who responded to lidocaine, even with a longer duration of effect (Lyttkens et al., 1984).

Procaine's high muscarinic affinity, together with the extensive distribution of muscarinic receptors that overlaps with brain regions activated by procaine, suggest that muscarinic activation contribute to procaine's emotional and sensory effects (Benson et al., 2004; including an overview of procaine's IC_{50} s for various systems). The finding that a structural analog of lidocaine's aromatic tail, 2,6-dimethylphenol, can block rat brain IIA sodium channels ($\text{Na}_v1.2_A$) with a potency (IC_{50} at 187 μM) comparable to lidocaine, indicates that this substituted benzene ring may constitute the smallest active compound of the lidocaine molecule that determines its state-dependent interaction with the sodium channel (Haeseler et al., 2002).

Symmetrical lidocaine dimers, in which the tertiary amines of the lidocaine moieties are linked by an alkylene chain, inhibit heterologously expressing rat $\text{Na}_v1.2_A$, human $\text{Na}_v1.5$ and rat $\text{Na}_v1.8$ channels with potencies 10- to 100-fold higher than lidocaine (Smith et al., 2006). Extracellularly administered QX-314, a permanently charged and therefore membrane impermeant quaternary derivative of lidocaine (see Section "GABA receptor/glycine receptor"), showed an IC_{50} for inhibition of muscarinic signaling 140-fold higher than lidocaine (18 nM versus 2.4 μM). Benzocaine, a permanently uncharged and therefore membrane permeant local anesthetic, was not an effective muscarinic blocker (IC_{50} at 1.2 mM) (Hollmann et al., 2000). Thus, small structural changes of local anesthetics can lead to great molecular functional changes and probably great changes of their clinical effects.

The potential of novel local anesthetics in suppression of tinnitus has not yet been investigated. Tetracaine (*N*- β -phenyl-ethyl-lidocaine) and sameidine (*N*-ethyl-1-hexyl-*N*-methyl-4-phenyl-4-piperidine carboxamide hydrochloride) may have a prolonged duration of action and less adverse effects compared to lidocaine (Hollmann et al., 2001). Also the use of liposomal delivery systems (e.g. Grant et al., 2004), combined with an intradermal application (Savastano, 2004), may prolong the effect of lidocaine on tinnitus.

Conclusions and possible directions for future research

There is evidence that lidocaine suppresses some forms of tinnitus in either the cochlea or the central auditory system, or in both locations, depending on the kind of tinnitus and the mode of application. There is also evidence that the IC may be a central target of lidocaine (Manabe et al., 1997; Eggermont, 2005). Various molecular channels and receptors, found in the auditory system and possibly connected to tinnitus, are affected by lidocaine. Sodium channels and partly muscarinic receptors have been found to have a high sensitivity to lidocaine, but there may also be other molecular targets.

Identification of molecular structures, which are involved in neuronal reorganization and neuroplasticity (Kaltenbach et al., 2005; Nitsche et al., 2005), and their (subtype) specific inhibitors could provide new pharmacological targets for treatment of tinnitus. Modeling the binding sites of local anesthetics, correlating the differences in binding interactions between several clinically useful drugs, and understanding the relationship between the binding region and the channel gating would make it possible to design drugs to target-specific isoforms and specific gating states (compare Fozzard et al., 2005). Research regarding finding treatments for tinnitus, as well as interdisciplinary research on local anesthetics and other tinnitus suppressing drugs at all neuronal levels, be it molecular, cellular or clinical, should be linked together. By using behavioral models of tinnitus in animals, it is possible to screen new drugs based on rational design (Smith and Darlington, 2005) (see Chapter 23). As illustrated above, changes in the structure of lidocaine resulted in large variations in its effects on the nervous system. In summary, understanding the specific mechanism of tinnitus inhibition by lidocaine may set the stage for new pharmacologic strategies.

Abbreviations

ABR	auditory brainstem response
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANFs	auditory nerve fibers
cAMP	3',5'-cyclic monophosphate
CAP	cochlear action potential
CHO	Chinese hamster ovary
CM	cochlear microphonics
CNS	central nervous system
DCN	dorsal cochlear nucleus
DPOAE	distortion product otoacoustic emission
fMRI	functional magnetic resonance imaging
GABA	γ -aminobutyric acid
IC	inferior colliculus
IC ₅₀	half-maximal inhibitory concentration

K _v	voltage-gated potassium
Na _v	voltage-gated sodium
NMDA	<i>N</i> -methyl-D-aspartate
OAEs	otoacoustic emissions
OHCs	outer hair cells
PET	positron emission tomography
rCBF	regional cerebral blood flow
SPECT	single photon emission-computed tomography
TEOAEs	transient-evoked otoacoustic emissions
TRPCs	transient receptor potential channels
TRPV1	transient receptor potential channel vanilloid 1
VR1	vanilloid receptor type 1

Acknowledgments

We would like to thank Akin Wingerter, Angela Doerschlag and Petra Altenhoff for critically reading earlier versions of the manuscript.

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CHAPTER 29

Antioxidants, minerals, vitamins, and herbal remedies in tinnitus therapy

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Abstract: The use of complementary and alternative medicine (CAM) is very popular in western countries and several CAM products are often used by individuals with tinnitus with or without medical guidance. CAM pharmacological approach to tinnitus today is mainly based on vitamins and minerals (dietary supplements), antioxidants, and herbal medications. Despite the popularity of CAM products, the evidence regarding their efficacy against tinnitus is in general scarce and their potential toxic effects are often underestimated or even neglected. In this paper the available literature on the efficacy of dietary supplements, antioxidants, and herbal medications against tinnitus is reviewed, and some of the major potential toxic effects are discussed. It is concluded that the use of CAM products in tinnitus therapy in general lack substantial scientific support, and that these substances are probably not clinically effective either. However, it is difficult to draw clear-cut conclusions regarding CAM pharmacological approach to tinnitus. In fact, the subjective nature of tinnitus and the reported variability in patient's response to therapy indicate that several non-pharmacological factors may be influencing drug effects, with the placebo effect playing a major role. Nevertheless, in view of the potential harm that may occur from inappropriate use of CAM products, physicians need to be aware of their principal characteristics with particular emphasis on toxicity and possibilities of interaction with prescription drugs.

Keywords: tinnitus; complementary and alternative medicine; *Ginkgo biloba*; antioxidants; vitamins

Introduction

Despite its prevalence and morbidity, tinnitus still remains an obscure disease involving diverse brain areas (Muhlau et al., 2006), and whose neurobiological bases are largely unknown (Eggermont, 2005). Mainly because of the subjective nature of the disorder and our lack of knowledge of its pathophysiology, treatment of tinnitus has been limited, controversial, and quite often unsuccessful

(Puel et al., 2002; Henry et al., 2005). Pharmacological treatment of tinnitus in particular, has proved to be a difficult task although the effect on tinnitus of many substances has been studied and some used to alleviate tinnitus (Simpson and Davies, 1999). However, there are presently no agents specifically recommended to this purpose (Smith and Darlington, 2005) (see also Chapter 23). Commonly prescribed drugs for tinnitus include sedatives, anticonvulsants, anti depressants, local anesthetics, antihistamines, antipsychotic, and *botulinum* toxin A: all providing mixed or inconsistent benefits (Patterson and Balough, 2006).

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Several forms of complementary and alternative medicine (CAM) are becoming increasingly popular in western countries (Goldstein et al., 2005), and are often selected by individuals with tinnitus with or without professional guidance (Simpson et al., 1998; Hu, 2004; Ventegodt et al., 2004). CAM has been defined as: “a group of diverse medical and health care systems, practices and products that are not presently considered to be part of conventional medicine” (NIH, 2007). Several hypotheses have been tested to understand the reasons for alternative care use among which are, poorer health status, anxiety, and chronic pain, together with a high education level and a holistic orientation to health (Astin, 1998; Lee et al., 2004). However, other factors such as dissatisfaction with conventional medicine, the feeling of despair about their problem, and the desire to play a more active role in their own treatment cannot be ruled out (Caspi et al., 2004).

Despite the recent change of attitude of the medical class toward CAM (Wahner-Roedler et al., 2006), many patients will begin such different therapeutic approach without medical guidance and are often reluctant to discuss CAM with their own physician (Cauffield, 2000; Howell et al., 2006; Vickers et al., 2006). As a consequence, nowadays the major sources of CAM-related information are the media, other patients, and (in particular) the Internet. A remarkable number of people in western countries get medical information through the Internet (Diaz et al., 2002; Murray et al., 2003; Pull, 2006), but the quality of such online health information is difficult to assess (Morris and Avorn, 2003; Walji et al., 2004; Bernstam et al., 2005). Regarding tinnitus, the Internet provides much CAM-related information ranging from relaxation techniques to drug treatment.

Unconventional pharmacological approach to tinnitus today is mainly based on the use of dietary supplements (in form of vitamins and minerals), antioxidants, and herbal medications.

Vitamins and minerals

With a few exceptions, such as vitamin D, lack of vitamins to an extent that cause sign and

symptoms of disease are uncommon in Western World. Despite this relative uncommonness of avitaminoses, nutritional supplements in the form of vitamins and minerals are extremely popular in western countries; it is estimated that members of 70% of American households take vitamins and annual spending on vitamins reached \$7 billion last year, according to industry figures. Vitamins and mineral supplements are commonly used to enhance health status and to prevent chronic diseases. Despite such a wide use, a growing body of evidence is now seriously questioning the benefit of the use of multivitamins and mineral supplement (Douglas et al., 2004; Huang et al., 2006; Stephen and Avenell, 2006). Serious concerns are also being raised about the safety of these substances (Timbo et al., 2006) and in November 2004, U.S. Food and Drug Administration (FDA) announced major regulatory initiatives for dietary supplements. So far, dietary supplement manufacturers have only been required to show proof of safety and lawfulness and not proof of effectiveness for their products (DeAngelis and Fontanarosa, 2003), but the FDA regulatory initiatives clearly state the need for measures to protect consumers against false, misleading, and unsubstantiated claims. The American Heart Association has stated that, “vitamins or mineral supplements aren’t a substitute for a balanced nutritious diet”.

Almost all available CAM formulations for treating tinnitus do contain several vitamins and minerals in various doses and formulations. Most represented substances are: vitamin A, B1, B3, B6, B9, B12, C, E, magnesium, calcium, potassium, manganese, selenium, and zinc. The evidence regarding the beneficial effect of the use of these substances for the treatment of tinnitus, in people with normal nutritional status, has mostly been anecdotal and empirical, and (Asher et al., 2001) none has been shown to be significantly beneficial when tested in properly designed clinical studies (Paaske et al., 1991; Arda et al., 2003; Seidman and Babu, 2003; Markou et al., 2004; Karkos et al., 2006). Studies of the potential toxic effects of these substances have been largely neglected or the results underestimated (Timbo et al., 2006). Recently, the UK Food Standard Agency (2003) in response to growing concerns over possible risk of

dietary supplement use (Willett and Stampfer, 2001), issued a detailed review of the available evidence on safety of many vitamins and minerals (Expert Group on Vitamins and Minerals, 2003). Reviewed substances were either known as essential to human health or just available on the market as dietary supplement. Indeed, the report of the Expert Group provides evidence that several vitamins and minerals may exert a wide range of toxic effects both for acute and chronic intake at high doses. In particular, advice is being given on several substances including many that have been used for treatment of tinnitus such as: iron, manganese, phosphorus, potassium, magnesium, vitamin B6, vitamin A, vitamin C, and vitamin E (Seidman and Babu, 2003).

Antioxidants

Under physiological conditions, free radicals are part of the normal cellular redox state and their potential toxicity is tightly controlled by the cellular antioxidant system (Droge, 2002). However, in certain conditions such as ischemia-reperfusion injury, free radicals production can overcome the antioxidant capability of the affected tissue inducing damage to biological structures eventually leading to cell death (Molyneux et al., 2002). Oxidative harm to cellular components has been linked to several physiological processes such as inflammation and aging (Barja, 2004), as well as to the pathophysiology of many diseases ranging from cardiovascular and neurological degenerative diseases to cancer (Loft and Poulsen, 1996; Calabrese et al., 2005). This correlation between oxidative stress and pathology formed the rationale for the use of antioxidants to prevent diseases and slow down the advance of aging. In particular, antioxidants may provide protection against oxidative damage by acting as a reducing agent, counteracting overproduction of reactive species, and preserving biological structures. Unfortunately, despite such a plausible theory and a large use of antioxidant by the population, the results of clinical trials in several fields so far have been largely controversial or inconsistent (Maxwell, 1999; Vivekananthan et al., 2003; Dangour et al., 2004;

Loft and Moller, 2006). Concerns have also been raised regarding the long-term effects of administration of antioxidants to healthy people. When it is considered that the cell redox system has evolved to maintain a finely tuned homeostatic state, the question of whether long term “brute-force” use of antioxidant agents may be inappropriate and interfere with cellular physiology, does not appear out of scope.

Oxidative harm has been implicated in the pathogenesis of ototoxic lesions due to aminoglycoside antibacterial and platinum-based chemotherapeutic drugs, and several attempt have been made to protect cochlear cells from reactive species with antioxidants (Rybak and Whitworth, 2005). Despite the widespread use of antioxidants in CAM pharmacological approach to tinnitus therapy, the evidence for involvement of reactive oxygen species in tinnitus pathophysiology are rather scarce and conflicting. There is some evidence that severe psychological stress may cause oxidative damage in vivo (Liu et al., 1996; Sivonova et al., 2004). Indeed some author did explore the possibility that the severe emotional distress often perceived by tinnitus sufferers could lead to an increased production of reactive species, but their results are still uncertain at best (Neri et al., 2006; Khan et al., 2007). It could be tentatively concluded that although antioxidants may not be a therapy for tinnitus per se, their use may be considered as a supplemental treatment for patients undergoing therapy with ototoxic drugs; nevertheless clinical studies are needed to better assess antioxidants protective role.

Herbal medications

Opposite to the general belief, herbal medications are drugs in every sense of the word, able to exert both therapeutic and toxic effects. In fact, the essential difference between herbal and pharmaceutical drugs is that while the last are available in a chemically pure state, herbal drugs are in form of phytocomplexes: a mixture of plant-derived substances that is likely to contain many active ingredients that are biologically active. The use and sales of herbal medications in western countries

have increased dramatically over the past years, and several different reasons may account for this phenomenon (Cauffield, 2000). Still, along with the fact that herbs are perceived by many patients as being “natural” and therefore safer than pharmaceutical drugs, it must be also considered that herbal medications are often as efficacious as their synthetic counterpart (Ernst, 2003; Szegedi et al., 2005). Unfortunately, only a small fraction of all used medicinal plants has been tested in rigorous clinical trials, and therefore the information regarding the efficacy and safety of these substances is often anecdotal or empirical (De Smet, 2002, Ferner and Beard, 2005; Wolsko et al., 2005). Remarkably, the French pharmacopeia lists herbal medication used in therapy, including both clinically tested herbs and those used out of tradition, describing their useful properties and their toxicological profile.

With regard to tinnitus therapy, several herbs have been used with mixed results. *Ginkgo biloba* leaves have been used for centuries in Chinese traditional medicine for the treatment of asthma and bronchitis. In western countries, *Ginkgo biloba* is commonly available in the form of leaf extracts, which in Europe and in the United States are among the most widely used and appreciated herbal medications (Spinella, 2001). Ginkgo extract contains two main pharmacologically active substances, flavonoid glycosides and terpene lactones, responsible for many biological effects such as neuroprotection, interaction with several neurotransmitter systems, and improvement of microcirculation via inhibition of the function of platelet-activating factor (MacLennan et al., 2002; Ponto and Schultz, 2003). Because of this complex interactions many bodily functions have been reported, including improvement of memory, cognition, sexual function, and protection against stress-induced learning deficit (Spinella, 2001; Birks and Grimley, 2007). Ginkgo-based products are also easily accessible, relatively inexpensive, and with a favorable safety profile (Bent et al., 2005). Ginkgo extracts have been proposed as cognitive enhancers and for the treatment of a large number of pathologies of the central nervous system, including tinnitus (Jastreboff et al., 1997; Logani et al., 2000; Birks and Grimley, 2007;

MacLennan et al., 2002). Several clinical studies have been published in recent years demonstrating a lack of a beneficial effect of Ginkgo extracts on tinnitus (Hilton and Stuart, 2004; Smith et al., 2005). Nevertheless, owing to the complex pharmacological profile of Ginkgo, its real therapeutic value in tinnitus therapy as a whole is still uncertain (Drew and Davies, 2001), and more rigorous work on the subject is needed.

Several other herbs have been proposed for tinnitus therapy, but none of them has been tested in rigorous trials; a few of them such as *Cimicifuga racemosa*, *Cornus officinalis*, *Verbascum densiflorum*, and Yoku-kan-san have received some scientific support (Seidman and Babu, 2003; Okamoto et al., 2005), but the evidence regarding efficacy against tinnitus and safety is, at best, anecdotal for the majority such as *Rhodiola rosea*, *Hydrastis canadensis*, *Sesamum indicum* (seeds), *Heliantus annus* (seeds), and many more others.

Conclusions

On the basis of the available data, it may be concluded that use of vitamins, minerals, antioxidants, and herbal medicinal products in tinnitus therapy in general lack sound scientific support, and that these substances are probably not clinically effective either. It could also be inferred that the use of these substances in tinnitus therapy may even be dangerous for the patient because of side effects, in the form of intrinsic toxicity, and waste of money while pursuing an ineffective treatment (Brown et al., 2002; Eidelman et al., 2004; Smith et al., 2005). The use of such substances in tinnitus therapy (as well as in the treatment of many other difficult or obscure diseases) is often promoted by non-medical publications such as the Wellness Press, and through various corporate-interest hype in direct opposition to more orthodox medical treatment.

In spite of the scarce evidence in favor of the role of vitamins, minerals, antioxidant, and herbs in tinnitus therapy, judging from the actual trends it is commonsense to predict that the use of these substances will not decrease in the near future; on the contrary it will most probably increase. Therefore, in order to make informed clinical decisions,

physicians need to be well aware of the possible therapeutic role of these substances, along with their pharmacological and toxicological characteristics. In fact, nutritional supplements, antioxidants and herbal medicinal products share the peculiar status of being biologically active substances commonly perceived by the public as “non-drugs”, therefore considered harmless and treated as such (Marcus and Snodgrass, 2005; Earnst, 2002). Unfortunately there is reason to be concerned about the potential adverse effects of some of these substances, especially because these “non-drugs” are generally self prescribed, taken without medical supervision, often not reported during medical consult (Howell et al., 2006) and often combined with prescription pharmaceutical drugs. This last issue is of particular importance when considering that there is clear evidence that some herbal products can interact with prescription drugs in different ways and through several mechanisms modify their clinical and/or toxicological profile (Ioannides, 2002; Bressler, 2005; van den Bout-van den Beukel et al., 2006; De Smet, 2006). Apart from the toxicological profile of each agent, other relevant medical problems include the increasingly reported pollution of herbal products with various chemicals including pesticides and heavy metals (Saper et al., 2004; Durgnat et al., 2005; Geraldine et al., 2006), and the fact that because of the lack of unequivocal specific regulations, substance type and concentrations often do markedly differ from label claims and varies among different lots of the same product (Gurley et al., 2000; Krochmal et al., 2004; Tam et al., 2006).

It is important to understand that often in spite of scientific evidence, and mainly because of the peculiar nature of tinnitus, its obscure pathophysiology, and its complex relationships with patient’s personality and psychological status (Halford and Anderson, 1991; Hiller and Goebel, 1992; Alpini and Cesarani, 2006; Hebert and Lupien, 2007) it is difficult to draw definitive and clear-cut conclusions regarding which pharmacological treatment would be beneficial, both in its more orthodox medical approach and in its complementary and alternative form (see Chapter 1). Nevertheless, in view of the scarce evidence

available and the potential harm obtainable from inappropriate use of some nutritional supplements, antioxidants, and herbal products, physicians need to be aware of their principal characteristics with particular emphasis on toxicity.

Abbreviations

CAM	complementary and alternative medicine
FDA	Food and Drug Administration

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CHAPTER 30

Melatonin

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Abstract: Melatonin is a neurohormone that is secreted by the pineal gland and known to impact the sleep-wake cycle. Melatonin is regarded to be a safe and natural sleep aid. Since many people with tinnitus suffer sleep disturbance, melatonin has been studied as a therapeutic agent for tinnitus. A review of the literature suggests that melatonin has a beneficial effect on tinnitus, especially for patients with sleep disturbance, but it does not seem to modify the strength or frequency of the tinnitus.

Keywords: tinnitus; melatonin; sleep-wake cycle; neurohormone

Description of melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is the primary secretory product of the pineal gland (Reiter, 2003). It has been linked to a variety of functions in humans, including regulation of circadian (Malpoux et al., 2001) and seasonal rhythms (Reiter, 1993), immune function (Guerrero and Reiter, 2002), retinal physiology (Dubocovich et al., 1999), tumor inhibition (Blask et al., 2002) and it has been found to be a free radical scavenger and antioxidant (Reiter et al., 2002; Tan et al., 2002). The major regulator of melatonin synthesis is the light/dark cycle with melatonin being synthesized during the dark. The amount of melatonin produced is genetically determined and decreases as we age. Melatonin is released directly into the third ventricle and is not stored within the gland (Arendt, 2000). The introduction of artificial light at night has greatly altered the amount of melatonin produced (Wehr, 2001).

Melatonin exerts its influence over the organism in many ways. It has both receptor-mediated and receptor-independent actions. While it is classified as a hormone and acts in typical endocrine ways, it also has autocrine and paracrine functions. Melatonin works at the level of the suprachiasmatic nuclei (SCN) to regulate and synchronize the internal biological clock. It is widely believed that melatonin does not work as a hypnotic or a soporific (drug that causes sleep) but rather by regulating the circadian clock (Kennaway and Wright, 2002). In the elderly, melatonin has also been found to improve sleep in those with insomnia, restless leg syndrome, REM-sleep-disordered behavior, delayed sleep phase syndrome, manic patients, and those with fibromyalgia (Cardinali et al., 2002). To improve sleep, melatonin should be taken approximately 30 min prior to bedtime and it may take 1 month or more before improved sleep is achieved (Garfinkel et al., 1995).

Clinical studies

A questionnaire survey among 10,216 elderly individuals in northern Sweden showed that 15%

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of the men and 12% of the women reported to have tinnitus (Asplund, 2003). Poor sleep was reported by 14% of the men and 28% of the women. Among individuals with tinnitus, poor sleep and frequent waking were common in both sexes, while difficulties in falling asleep after awakening at night were reported more often by women. Daytime sleepiness (DS) was more common in individuals with tinnitus and the frequency was even more increased in those with both tinnitus and poor sleep. There was no further increase in DS in men and women on sleep medication. The author concludes that DS in elderly persons with tinnitus may be due not only to the tiring effect of the annoying sound itself but also the negative effect of tinnitus on sleep.

A double-blind, placebo-controlled crossover study of the effect of melatonin on tinnitus showed no statistical difference between *Tinnitus Handicap Inventory* (THI) scores after placebo (26.4) and after melatonin (26.1) (Rosenberg et al., 1998). Both scores were significantly different from the pretreatment scores of 33.9. The study was initiated after several of their patients reported improvement in tinnitus following the use of melatonin as a sleep aid. A total of 30 individuals were enrolled in the study and prior to initiation of therapy, participants underwent audiometry and tinnitus matching and they all completed the THI, a 25-item, self-report instrument that measures the physical, functional, and emotional problems related to tinnitus (Newman et al., 1996). Scores range from 0 to 100 with a maximum of 100 representing worse possible impairment. Individuals were given a 30-day supply of either 3 mg melatonin or placebo and instructed to take one pill nightly 1–2 h before sleep. After the initial 30-day participation, participants underwent a 7-day washout period during which time no medication was taken. After the washout period, participants received the second 30-day supply of medications. Participants were questioned after the first 30-day period and again after the second 30-day period.

Of the 30 participants enrolled in the study, 23 (77%) completed both phases of the study. When the participants were asked if, overall, their

tinnitus was improved after the medication they had just completed, 9/23 (39%) taking melatonin reportedly affirmatively, while 4/23 (17%) taking placebo reported affirmatively. This difference of 22 percentage points was not statistically significant ($p = 0.06$). However, among the 15 participants who reported trouble sleeping as a result of their tinnitus, 7/15 (47%) reported improvement after taking melatonin as compared with 3/15 (20%) taking placebo. This difference of 27 percentage points achieved statistical significance ($p = 0.04$). When asked if they would recommend the pill to someone with tinnitus, 8/23 (35%) said yes when they were taking melatonin, while 4/23 (12%) said yes while taking placebo ($p = 0.16$). There were no significant side effects related to melatonin.

A prospective open-label study of the effect of melatonin on troublesome, unilateral or bilateral, idiopathic nonpulsatile tinnitus showed improvement in tinnitus that was related to improvement in sleep (Megwalu et al., 2006). The study population consisted of patients seen at a tertiary medical center between the ages of 18 and 70 with tinnitus of 6 month's duration or greater. Twenty patients were enrolled in the study and 18 patients (75%) completed the entire 8 weeks. The patients took 3 mg of melatonin, one pill nightly 1–2 h before bedtime for 4 weeks. This was followed by an additional 4 weeks of observation during which time the patients received no melatonin. The THI and the *Pittsburgh Sleep Quality Index* (PSQI) were administered at the beginning of the study (week 0) and at weeks 2, 4, 6, and 8 of the study. Primary outcome measures were the changes in THI and PSQI between weeks 0 and 4, and between weeks 0 and 8. The secondary outcome measure was the association between the change in THI and the change in PSQI.

There was a statistically significant decrease in the mean THI score of 6.6 between weeks 0 and 4 (95% CI 1.4–8.8; $p = 0.02$) and 7.8 points (statistically significant; 95% CI 3.7–12.9; $p = 0.006$) between weeks 0 and 8. Neither change score was as great as the predetermined value of 10 for clinical significance, although the upper 95%

CI did exceed 10 for the difference between week 0 and week 8. The mean *PSQI* decreased 2.9 points between weeks 0 and 4 (95% CI 1.6–4.2; $p < 0.0001$) and the mean *PSQI* decreased 2.5 points between weeks 0 and 8 (95% CI 1.3–3.7; $p = 0.0003$). These decreases were considered clinically significant since they were equal to or greater than the predetermined value of 2.5.

The change in *PSQI* was associated with the change in *THI* between weeks 0 and 4 (correlation coefficient = 0.46, $p = 0.04$); between weeks 0 and 8 the correlation coefficient = 0.28, $p = 0.26$. The average change in *PSQI* among those nine patients who had a clinically significant decrease in *THI* (equal to or greater than 10) in the first 4 weeks was 3.9 points. There was an association between the *PSQI* at week 0 and the change in the *PSQI* in the first 4 weeks (correlation coefficient = 0.52, $p = 0.02$), indicating that patients with greater sleep disturbance had greater response to melatonin regarding their sleep. However, there was no association between the *THI* at week 0 and the change in the *THI* in the first 4 weeks (correlation coefficient = -0.32 , $p = 0.16$) indicating that the response to melatonin was unrelated to the severity of the tinnitus before the beginning of the study. Melatonin was well tolerated by all patients. No adverse effects were reported by any of the patients.

Conclusions

Multiple studies (Rosenberg et al., 1998; Asplund, 2003; Megwalu et al., 2006), suggest that melatonin is a safe and effective treatment for patients with idiopathic tinnitus, especially those with sleep disturbance.

Abbreviations

CI	confidence interval
PSQI	Pittsburgh sleep quality index
THI	tinnitus handicap inventory

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CHAPTER 31

Botulinum toxin for the treatment of somatic tinnitus

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Abstract: Subjective tinnitus is an auditory sensation experienced in the absence of external or internal acoustic stimuli. It causes significant morbidity and can progress to a chronic debilitating condition. Somatic tinnitus is tinnitus that can be modulated by stimulation of the somatic sensory system. It occurs because of interactions between the auditory and the somatosensory system that may occur at several levels of the central nervous system. In the present chapter, we discuss how botulinum toxin can improve tinnitus and discuss the mechanism of its action, and how it relates to its effects on chronic pain.

Keywords: somatic tinnitus; botulinum toxin; autonomic pathway; headache; dorsal cochlear nucleus

Introduction

Tinnitus is described as a perception of sound in an absence of external and internal sound stimuli. It can be unilateral or bilateral and may be the first or only symptom of a disease process in auditory system or in the central nervous system (CNS).

While the pathophysiology of the different forms of tinnitus remains poorly understood, there is increasing evidence from electrophysiologic and functional neuroimaging studies of an association between severe chronic tinnitus and abnormal functioning of the CNS (Møller, 2003). Specifically, abnormal processing within the auditory pathway may account for phantom perceptions of sound in the central auditory system. In detail neuroimaging studies have demonstrated that tinnitus is associated with increased activity of the inferior colliculus (Melcher et al., 2000), the thalamus (Reyes et al., 2002), and the auditory cortex (Arnold et al., 1996; Lockwood et al., 1999;

Mirz et al., 1999; Reyes et al., 2002). It is assumed that chronic tinnitus is caused by expression of neural plasticity (see Chapter 3) and by homeostatic mechanisms. Chronic severe tinnitus has many similarities with chronic pain (Rauschecker, 1999; Møller, 2003) (see Chapter 4). Animal models of tinnitus suggest that Ca^{2+} -signaling pathways as well as an imbalance between the GABAergic and glutamatergic system are among the involved mechanisms (Eggermont, 2005) (see Chapter 2) in some forms of tinnitus.

Somatic tinnitus

The finding that people can develop tinnitus from forceful head and neck contractions is an example of somatic tinnitus. Temporomandibular joint disorders (TMJ) are also often associated with tinnitus (Morgan, 1992), thus another example of somatic tinnitus. Effective treatment of the underlying disorder may resolve somatic tinnitus in some cases, but not in others (Levine, 2004). The neural mechanisms of somatic tinnitus have been

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described elsewhere in this volume (Chapters 10 and 17).

Likewise, there are some reports suggesting that somatic stimulation of the head or upper neck can suppress tinnitus through the somatic pathway (Levine, 2004); that is the most important hypothesis, which supports some treatment strategies such as benzodiazepines, acupuncture, antidepressants, biofeedback, and electrical stimulation as muscle relaxing strategies. Another way to treat tinnitus is by administrations of drugs that act as neuromodulators such as selective serotonin reuptake inhibitors (SSRIs), anticonvulsants, or benzodiazepines.

Botulinum toxin type A

Botulinum toxin type A (BoNT-A) is a focally administered neurotoxin, which inhibits the release of acetylcholine at the neuromuscular junction (Simpson, 1986) and is used therapeutically in disorders characterized by muscle hyperactivity, including movement disorders, dystonia, spasticity, cerebral palsy, gastrointestinal, and urological disorders. BoNT-A is also used in cosmetics to diminish wrinkle and frown lines because of its known paralytic effect (Klein, 2001). It should be noted that botulinum toxin has system effects that may affect cardiovascular reflexes (Girlanda et al., 1992).

In vitro and in vivo studies (Blersch et al., 2002) have demonstrated that BoNT-A inhibits the release of nociceptive mediators such as glutamate, substance P, and calcitonin gene related peptide (CGRP) from nociceptive fibers (Dolly, 2003), suggesting that BoNT-A may have a direct antinociceptive action through its effects on the autonomic nervous system in addition to its neuromuscular action (Aoki, 2003; Cui et al., 2004; Durham and Cady, 2004). Moreover, through a peripheral mechanism, BoNT-A has also been shown to inhibit central sensitization of central trigeminovascular neurons (Oshinsky et al., 2004), which is felt to be an integral part in the development, progression, and maintenance of migraine (Silberstein et al., 2000; Burstein and Jakubowsky, 2004). Central sensitization is also

considered to be a potential mechanism underlying the development of chronic daily headache in patients with migraine. Several clinical trials also suggest that BoNT-A may be an effective and safe prophylactic headache medication in the treatment of migraine and other headache disorders (Dodick et al., 2005). Thus, evidence has been presented that the blockage of the autonomic pathway, and not just the paralytic effect contribute to the ability of BoNT-A to control headaches, chronic neuropathic pain, and migraines (Silberstein et al., 2000; Aoki, 2003; Barrientos and Chana, 2003). Because of the similarities between tinnitus and pain, we have investigated the effect of BoNT-A on tinnitus.

Botulinum toxin in treatment of tinnitus

A prospective double-blind study of the effect of BoNT-A in 30 patients with tinnitus (Stidham et al., 2005) in which 26 patients completed both injections and were included in the analysis, 7 patients improved, 3 worsened, and 16 were unchanged; whereas following placebo, 2 patients improved, 7 worsened, and 17 were unchanged. In this study BoNT-A was injected in the arm and placebo with saline injection 4 months later of 26 of the participants. In 26 of the participants, the other arm was first injected with saline and then BoNT-A 4 months later. Tinnitus and hearing were evaluated using questionnaires similar to the tinnitus handicap inventory (THI). Audiograms, pure tone average-2 (PTA-2) and speech discrimination scores (SDS) were obtained prior to the first and second injection for all participants. The technique used to inject BoNT-A or placebo were into three sites around the ear; 1 cm above superior aspect of auricle, 1 cm behind auricle at the 2 o'clock position, and 1 cm behind auricle at the 5 o'clock position (Stidham, 2005).

When tinnitus was classified as "better," "worse," or "same" (global clinical impression estimated by patients) the treatment and placebo groups were statistically significant ($p < 0.05$) different. Also with an objective measure as THI, the scores decreased significantly between pretreatment and 4 months post BoNT-A injection

($p = 0.04$). The results of this study suggest that administration of BoNT-A can play a role in tinnitus management.

Conclusions

In conclusion, the injection of BoNT-A essentially works through a reduction of peripheral inputs from cervical, temporal, frontal, and periauricular muscles. This mechanism can produce a reduction of the activation of the medullary-somatosensory nucleus (MSN) or Nucleus Z to the dorsal cochlear nucleus (DCN) pathway that is effective in the management of chronic headache, and therefore it could also explain tinnitus relief.

Abbreviations

BoNT-A	botulinum toxin type A
CGRP	calcitonin gene related peptide
CNS	central nervous system
DCN	dorsal cochlear nucleus
GABA	gamma amino butyric acid
MSN	medullary-somatosensory nucleus
PTA-2	pure tone average-2
SDS	speech discrimination scores
SSRIs	selective serotonin reuptake inhibitors
THI	tinnitus handicap inventory
TMJ	temporomandibular joint disorders

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CHAPTER 32

Hearing aids for the treatment of tinnitus

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Abstract: Clinical evidence shows that the use of hearing aids in tinnitus patients provides two benefits: it makes the patient less aware of the tinnitus and it improves communication by reducing the annoying sensation that sounds and voices are masked by the tinnitus. Hearing loss reduces stimulation from external sounds resulting in increased awareness of tinnitus and deprivation of input may change the function of structures of the auditory pathways. Tinnitus is often caused by expression of neural plasticity evoked by deprivation of auditory input. With hearing aid amplification, external sounds can provide sufficient activation of the auditory nervous system to reduce the tinnitus perception and it may elicit expression of neural plasticity that can reprogram the auditory nervous system and thereby have a long-term beneficial effect on tinnitus by restoring neural function. To obtain the best results, hearing aids should be fitted to both ears, use an open ear aid with the widest amplification band, and disabled noise reducing controls. In some cases a combination device would be preferable. The conditions required in order to obtain good results include not only the use of devices, but above all, their adaptation to the needs of the single patient, by counseling and customization. Wearing the hearing aid must become second nature to the patient even though it is only one element of the therapy.

Keywords: hearing aid; sound therapy; sound generator; tinnitus; hearing loss; open ear device

Introduction

Epidemiological studies show that approximately 50% of individuals with hearing loss also have tinnitus (Davis, 1998). Other studies show other values, thus Sheldrake and Jastreboff (2004) showed that approximately 70% of individuals with hearing problems have tinnitus. The incidence of tinnitus is greater in the population that consults an ear nose and throat (ENT) specialist (Davis and Refaie, 2000). For this reason, the use

of hearing aids is justified as a means to reduce the effects of the tinnitus.

Saltzman and Ersner (1947) showed that patients with tinnitus benefited from using hearing aids. These results were subsequently confirmed by other studies (Kiessling, 1980; Stacey, 1980; Brooks and Bulmer, 1981; Miller, 1981; Melin et al., 1987). In literature it reported that approximately 50% of patients utilizing hearing aids experienced relief from the tinnitus (Surr et al., 1985). In later studies, Surr et al. (1999) reported an average improvement of approximately 10%, only 6 weeks after the hearing aid was fitted. On the other hand, Melin et al. (1987) concluded that hearing aids were not an effective means for

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reducing tinnitus. It must nevertheless be remembered that the hearing aids of that time were linear analog devices that were much less flexible in terms of their adaptability to the needs of the patient than modern digital hearing aids, and thus these old types of hearing aids were not suitable for patients with slight to medium levels of hearing loss or progressive hearing loss in the high-frequency range, which is often accompanied by tinnitus (Konig et al., 2006).

Folmer and Caroll (2006) compared 3 groups of 50 individuals with tinnitus using hearing aids, custom sound generator and other forms of acoustic therapy (music, relaxation CDs or the environmental sound machine). The participants that used hearing aids had hearing loss in the high-frequency range. After an average of 18 months after treatment, 70% of the participants who used hearing aids and 76% of those who used sound generator had improvements of their tinnitus. The participants in all groups reported a significant reduction ($p < 0.0001$) in their Tinnitus Severity Index (TSI) score.

Hearing aids or custom sound generators even reduced tinnitus in individuals with Ménière's disease (Herraiz et al., 2006a).

The authors own daily clinical experience — just like the experiences published (Sheldrake and Jastreboff, 2004) — has shown how the use of hearing aids provides two benefits: (1) it makes the patient less aware of the tinnitus, or even masks the tinnitus itself; (2) it improves communication and reduces the annoying sensation that sounds and voices are masked by the tinnitus.

Neurophysiological rationales for using hearing aids

The rationale behind the treatment of tinnitus by hearing aids is based on two complementary assumptions:

- (1) By increasing the level of ambient noise perceived by the patient, prosthetic amplification reduces or eliminates the contrast between endogenous sound (the tinnitus) and the silence caused by hearing loss (Frachet et al., 2004). This effect can be achieved by sound therapy, both in total

masking (Vernon and Meikle, 2000) or in partial masking of the tinnitus (mixing point) utilized in TRT, in accordance with Jastreboff's neurophysiological model of tinnitus (Jastreboff, 1999). The hearing aid is a useful instrument for habituating the patient to the perception of the noise of the tinnitus. In this way, the tinnitus gradually becomes less intrusive and thus less annoying: less attention is paid to the tinnitus, which is relegated to the category of minor stimuli, thus facilitating gradual habituation (Sheldrake and Jastreboff, 2004).

- (2) Most forms of tinnitus occur together with slight hearing loss, or hearing loss that is limited to the high frequencies (Konig et al., 2006). Hearing loss cause deprivation of input, which can lead to tinnitus through expression of neural plasticity (see Chapter 3) and it has been shown that it can lead to hyperactivity of the neurons in the auditory pathways (Kaltenbach, 2006) (see Chapter 9). Even a slight loss can cause changes in the function of parts of the auditory nervous system. Several studies have shown that changes caused by deprivation can be reversed by appropriate sound stimulation (Norena and Eggermont, 2006). Hearing aids are beneficial because they can restore auditory input and can stimulate cerebral plasticity (Gabriel et al., 2006). A mathematical model (Schaette and Kempster, 2006) has also been published, which predicts how tinnitus combined with neural hyperactivity could be reduced by means of adequate stimulation. The second rationale arises from this, maintaining that, thanks to the hearing aid, it is possible to stimulate cerebral plasticity and, at least, partly re-establish the proper functioning of the auditory nerve pathways, limiting one of the probable causes of tinnitus.

Hearing aids can facilitate the use of music in therapy of individuals with tinnitus and redirect attention toward complex and more interesting sounds (Searchfield, 2005) (see also Chapter 43).

The hearing aid as an instrument for the treatment of tinnitus

Whenever possible, the fitting should be done with open ear hearing aids. The importance of utilizing hearing aids with large ventilation (Sheldrake and Jastreboff, 2004; Searchfield, 2005) has become more evident with the availability of open ear devices. The partial occlusion of the external auditory canal can lead to dissatisfaction with the use of the device and, in some cases, even lead to an increase in the perception of the tinnitus. The open fitting hearing aids also provide extended stimulation even at the higher frequencies, in the tinnitus pitch area. In this way, it is possible to obtain a dual result: providing the sound enrichment necessary for developing habituation to sound therapy and stimulating the neural plasticity of the auditory pathways, as discussed previously. The fitting of open ear devices in the treatment of tinnitus has been shown (Del Bo et al., 2006) to be as effective, if not more so, than for custom sound generators.

Whenever possible, hearing aids should be fitted in both ears since this allows better spatial localization and understanding of verbal messages. Both of which are important factors that make an additional contribution to controlling tinnitus by activating the entire auditory nervous system. In patients with deafness in one ear (anacusis), the use of a contralateral routing of signals (CROS) solution is advisable: the rationale for this approach is provided by the multisensorial stimulation of the auditory system, a situation that facilitates adaptation to the tinnitus (Sheldrake and Jastreboff, 2004).

Modern digital hearing aids are very versatile and equipped with numerous functions to improve hearing comfort, which are not, however, always suitable for the treatment of tinnitus. Directional microphones often reduce the amplification at low frequencies and thus it is advisable to activate the omnidirectional microphone; in addition, for the same reasons outlined above, it is appropriate to increase the amplification of weak, low-frequency sounds deactivating expansion and lowering compression activation point as well as disabling the digital noise reduction circuit. Obviously these

modifications must only be made if they are compatible with patient comfort and user satisfaction.

When utilizing open ear hearing aids, Digital Feedback Cancellation should be activated. It must be a contra phase control and not notch filter, so as to avoid a lessening of amplification at high frequencies. It is also appropriate to use hearing aids with the widest possible high-frequency amplification band because many patients have high-frequency hearing loss and high-frequencies amplification can provide stimulation in the auditory pathway in the area of tinnitus pitch. The tinnitus associated with profound deafness can be treated advantageously by means of a cochlear implant (Matsushima et al., 1994; Mo et al., 2002; Rubinstein et al., 2003; Jastreboff and Hazell, 2004).

It has been estimated that 5% of patients who seek help for their tinnitus has normal hearing. For such patients custom sound generators are useful (Searchfield et al., 2002).

It is important always to recommend that the patient introduce environmental auditory enrichment, by using a table sound machine. Subjects with hearing loss and tinnitus can obtain an additional benefit from sound therapy by using a hearing aid with a built-in sound generator (combination instrument) (Frachet et al., 2004). In this case, the amplification of environmental signals is enriched by the addition of continuous stimulation from the hearing aid, with wide band sounds at a controlled level. In patients affected by transmission deafness following malformation of the outer and middle ear, use of a traditional hearing aid with custom ear mould is not advisable. According to Holgers and Hakansson (2002), 35% of these patients have tinnitus. In the aforementioned cases, the fitting of a bone-anchored hearing aid (BAHA) may be useful. Fitting the BAHA requires minor surgery that, in the adult patient, is normally done under local anesthesia (Tjellstrom et al., 2001). By using this type of hearing aid, we avoid any occlusion of the auditory canal and the patient is provided with a level of amplification suited to his level of hearing loss. Amplification can be used in the treatment of patients with tinnitus, in accordance with what has already been stated for traditional hearing aids.

The conditions required in order to obtain good results with hearing aid treatment for tinnitus include not only the use of technologically advanced devices, but above all, their adaptation to the needs of the patient, as well as counseling. The patient must be listened to, guided and kept informed, right from the diagnostic stage, throughout the setting up of the therapy and during the course of the adjustment and follow-up visits (Herraiz et al., 2006a, b). This will allow the therapist to understand the problems and attempt to resolve them, as far as possible, by appropriate fitting of the devices. This task involves all the technical and medical staff, which must always be able to respond to the patient's many requests for information with precision and in a coordinated manner.

Acknowledgment

Many thanks to Stella Forti for her help and precious work.

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CHAPTER 33

Cochlear implants and tinnitus

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Abstract: The clinical observation that multichannel intra-cochlear cochlear implants have a suppressive effect on tinnitus in profoundly deaf patients is supported by many published studies. Whilst there are problems with that literature, specifically in the way that tinnitus outcomes are reported, the finding of tinnitus benefit is consistent. New developments in this area include the use of functional imaging to investigate tinnitus suppression by cochlear implant stimulation and consideration of a reported worsening effect on tinnitus of binaural implantation. Following work on hearing aids, it is suggested that optimization of the benefit of monaural cochlear implantation on tinnitus in a tinnitus-specific electrode configuration might include the use of a low knee point compression algorithm and disabling directional microphone function: these strategies are potentially also of benefit in patients whose tinnitus results in sleep disturbance. Opportunities for stimulation strategies for tinnitus suppression that bypass speech processing are also identified.

Keywords: tinnitus; cochlear implant; auditory brainstem implant

Introduction

Clinicians working with cochlear implant patients have often reported that implant use can have a beneficial effect on tinnitus (Miyamoto and Bichey, 2003). Indeed, considerable published research supports this observation. Thus a recent review (Quaranta et al., 2004) identified 32 published papers (of which 12 were from the peer-review literature) that explicitly discussed the effect of cochlear implants on tinnitus. Whilst this body of literature has inconsistencies, it does provide useful material for a scientific consideration of tinnitus, and may potentially guide us towards optimizing the inhibitory effect of a cochlear implant on tinnitus. Further, it may facilitate the

development of novel treatment strategies for tinnitus that utilize electrical stimulation of the cochlea (auditory nerve).

The purpose of the present paper is to draw out the themes evident in published research in the area of cochlear implants and tinnitus, and then to consider developments in the field, specifically binaural cochlear implantation, modified electrode arrays and cochlear implantation for tinnitus in patients with unilateral severe profound sensorineural hearing loss (SNHL).

The prevalence of tinnitus in cochlear implant candidates

Many papers reporting series of patients undergoing cochlear implantation indicate the number reporting tinnitus, but unfortunately there are no

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consistent definitions of that tinnitus. One might therefore expect some authors to be reporting patients with any tinnitus experience at all, and others patients with tinnitus that was severe enough to be troublesome. Further, such papers have not utilized the validated questionnaires that are in regular use in the tinnitus field, such as the Tinnitus Handicap Inventory (THI) (Newman et al., 1996) or the Tinnitus Questionnaire (Hallam, 1996), so one is unable to determine the extent to which tinnitus is bothersome in this population.

Despite these concerns, there is relative consistency in the reported prevalence of tinnitus in patients about to undergo cochlear implantation. The existing data is summarized in Table 1, and indicates that in 18 research papers reporting a total of 1104 cochlear implant candidates, a range of prevalence data from 67 to 100% with a mean of 80% is demonstrated.

In general terms therefore one can observe that one in five of the patient population who have acquired severe to profound hearing loss or deafness either have tinnitus that is only mildly troublesome, or no tinnitus at all.

In this analysis papers have been considered that were published from 1990 to 2006. It should be

noted that candidacy criteria for cochlear implantation are changing, and becoming less constraining. In particular, patients with severe SNHL became considered as candidates during this time period, rather than only those with a profound hearing loss only being considered initially. Candidates with severe acquired SHNL may have differences in prevalence and severity of tinnitus than the traditional cohort: robust published data is not yet available in this regard.

Effect of surgery

The insertion of an intra-cochlear implant electrode is potentially traumatic to any remaining functional cochlear structures (Adunka and Kiefer, 2006), and is believed to involve both necrotic and apoptotic mechanisms of cell death (Eshraghi and Van de Water, 2006) and such electrode insertion may influence tinnitus. Intriguingly however, in the small number of papers which consider this issue there are indications that for some patients there may be an improvement in tinnitus associated with electrode insertion (Gibson, 1992; Kim et al., 1995; Greimel et al., 2002), though the positive expectations of the patient regarding the implant may be a factor in this regard. There are also reports of small numbers of patients in whom electrode insertion exacerbates tinnitus (> 10%) (Gibson, 1992) or precipitates it being heard for the first time (> 4%) (McKerrow et al., 1991; Tyler, 1994; Miyamoto et al., 1997). Changes in tinnitus pitch and timbre have also been reported (Souliere et al., 1992).

Effect of use of monaural intra-cochlear devices

Studies that have reported the effect on tinnitus of the use of monaural multichannel cochlear implants are summarized in Table 2. Whilst there are marked inconsistencies in the way that tinnitus outcomes are reported, it can be seen that for the overwhelming proportion of patients, cochlear implant use has a very significantly beneficial effect on tinnitus. The possibility that this is not only an auditory phenomenon but also linked with

Table 1. Prevalence of tinnitus in cochlear implant candidates

Author	Tinnitus prevalence (%)
Tyler and Kelsey (1990)	42/52 (81)
McKerrow et al. (1991)	6 (100)
Bredberg et al. (1992)	18/21 (86)
Souliere et al. (1992)	28/33 (85)
Gibson (1992)	42/52 (85)
Tyler (1994)	30/41 (73)
Kou et al. (1994)	14/23 (70)
Hazell et al. (1995)	202/256 (79)
Ito (1997)	54/60 (90)
Miyamoto et al. (1997)	48/64 (75)
Aschendorff et al. (1998)	32/47 (68)
Demajumdar et al. (1999)	80/99 (80)
Greimel et al. (2002)	26/39 (67)
McKinney et al. (2002)	46/56 (82)
Mo et al. (2002)	59/74 (80); 'troublesome' in 29 (35)
De Coninck et al. (2006)	59/91 (65)
Kompis et al. (2006)	44/61 (72)
Yonehara et al. (2006)	21/29 (72)

Table 2. The influence of multichannel cochlear implants upon tinnitus

Author	Cases	Type of implant	Tinnitus effect ipsilateral
Tyler and Kelsey (1990)	42	Mixed (single and multichannel)	34 (81%) improved 7 (17%) same 1 (2%) worse
McKerrow et al. (1991)	6	UCSF/Storz 4 channels	5 (83%) abolished 1 (17%) same
Souliere et al. (1992)	28	Multichannel (Nucleus)	20 (77%) improved
Gibson (1992)	41	Multichannel (Nucleus)	25 (61%) better 16 (39%) same
Tyler (1994)	30	Multichannel (Ineraid and Nucleus)	25 (83%) improved 5 (17%) same
Hazell et al. (1995)	127	Mixed	73/127 (57%) better 43/127 (44%) same 11/127 (9%) worse
Bredberg et al. (1992)	18	Mixed	Group data indicates statistically significant decrease in loudness and annoyance
Kou et al. (1994)	14	Nucleus 22 channel	12 (86%) partial or complete elimination of tinnitus when CI on 5 (36%) complete elimination 6 (26% of total series) developed tinnitus as a result of implant surgery
Kim et al. (1995)	13	Multichannel (Nucleus)	10 (77%) better 3 (23%) same
Ito (1997)	54	Multichannel (Nucleus)	40 (74%) very effective 10 (19%) effective 4 (7%) unchanged
Miyamoto et al. (1997)	48	Multichannel 55 (Nucleus and Clarion) Single channel 9	22 (46%) better 24 (50%) same 2 (4%) worse
Aschendorff et al. (1998)	32	Multichannel (Nucleus)	22 (69%) better 10 (31%) no change
Demajumdar et al. (1999)	80	Multichannel (Nucleus)	62 (78%) abolished
Ruckenstein et al. (2001)	38	Multichannel (Nucleus and Clarion)	17 (45%) abolished 19 (50%) reduced 3 (5%) unchanged
Greimel et al. (2002)	26	Not stated	15.4% abolished 26.7% decreased 50% unchanged
Mo et al. (2002)	59	Multichannel intracochlear	32 (54%) better 21 (36%) no change 5 (8%) worse 1 (2%) abolished
Daneshi et al. (2005)	20	Multichannel	11 (55%) complete inhibition 5 (25%) significant attenuation 4 (20%) no change
De Coninck et al. (2006)	91	Multichannel (Nucleus and Hires, Laura)	29% abolished 30% reduced loudness
Kompis et al. (2006)	44	Not stated	36 (72%) improved 2 (5%) unchanged 6 (13%) worsened 2 of 15 patients (15%) who do not have pre-operative tinnitus developed it in the first 6 months of device use
Yonehara et al. (2006)	21	Nucleus 24K	7 (33%) total suppression 8 (37%) partial suppression

Table 3. The influence of multichannel cochlear implants upon tinnitus in the contralateral ear

Authors	Contralateral improvement
McKerrow et al. (1991)	67%
Souliere et al. (1992)	42%
Hazell et al. (1995)	52% better
Kim et al. (1995)	71%
Fukuda and Mangabeira	20% suppressed
Albernaz (1998)	20% decreased
Demajumdar et al. (1999)	Tinnitus abolished in 14/70 (20%)
Yonehara et al. (2006)	86% “totally suppressed or decreased”

increased quality of life has been noted (McKinney et al., 2002, Mo et al., 2002).

Several trends have been observed. The first (Quaranta et al., 2004) is that intra-cochlear multichannel devices (cochlear implants appear to have a more positive effect on tinnitus than the initially available extracochlear single channel devices, which were also less effective in providing auditory abilities (House, 1976; Berliner et al., 1987).

Second, it appears that the use of a monaural cochlear implant may improve tinnitus in the contralateral ear (Quaranta et al., 2004). Data summarized in Table 3 indicate that for many patients, utilizing a cochlear implant in one ear can markedly reduce the perceived intensity of tinnitus in the contralateral ear. It has been suggested that this is due to masking (Battmer et al., 1989) or due to plastic reorganization of the auditory system, both of the ipsilateral and contralateral pathways, following cochlear implant use (Quaranta et al., 2004). Additionally, there is experimental evidence of the influence of contralateral auditory stimulation on neural activity evoked by sound in the ipsilateral pathways (Davis, 2005); this has been demonstrated to be both inhibitory (Ingham et al., 2006) and excitatory (Sumner et al., 2005).

The finding of contralateral inhibition of tinnitus disagrees with the prediction of Jastreboff (2000) that in a patient with tinnitus, asymmetric or unilateral sound stimulation should exacerbate tinnitus contralateral to that of stimulation. While it does not affect other aspects of Jastreboff’s

neurophysiological model of tinnitus (Jastreboff, 1990), and the benefit from the use of Tinnitus Retraining Therapy (Jastreboff and Hazell, 1993), it is a reminder that a particular model may not cover all aspects of the functions of a complex system such as the auditory nervous system and that model predictions may not be supported exactly by experimental or empirical evidence. This also applies to other models (Baguley, 2006) such as the model of psychological aspects of tinnitus described by Hallam et al. (1984).

Optimization

It should be noted that cochlear implant stimulation strategies are designed to optimize speech discrimination, but they may not be optimal for tinnitus inhibition (Andersson et al., 2005). There has been little preliminary work in this area. A study of two individuals with tinnitus who had cochlear implants by Dauman and Tyler (1993) attempted to identify the optimal stimulation rate and electrode location that was most effective in suppression of tinnitus. Rubinstein et al. (2003) studied the effect of electrical stimulation with 5000 pps pulse trains via cochlear implant in 3 individuals and via a transtympanic electrode in 11 individuals, and found that “between a third and a half of them achieve clinically significant tinnitus suppression without a sustained percept”. Vernon (2000) reported that masking with noise (6–14 kHz) via a Nucleus 22 cochlear implant was beneficial to an individual with bilateral tinnitus, leading to some residual inhibition lasting 2–3 min and some contralateral suppression. A preliminary report of the use of a commercialized extracochlear device delivering electrical stimulation to the oval window showed beneficial effect on tinnitus (Frachet et al., 2006). This remains an interesting area.

Aspects of programming of a hearing aid for optimal suppression of tinnitus benefit may have some relevance for cochlear implant programming (see Chapter 32). Searchfield (2005) suggests that low compression knee points should be used when programming hearing aids for tinnitus relief and directional microphone technology should be

disabled. Both of these changes will increase the amount of ambient and environmental sound that is delivered to the ear by the hearing aid. These tactics are variously feasible in current cochlear implant devices.

If a patient has sleep disturbance and troublesome tinnitus (see Chapter 21), one might consider programming a cochlear implant device for night-time use. There are two possibilities: first one might utilize a program that facilitates night-time use of an environmental sound generator, with sounds such as wind, rain, or the ocean — devices that have been shown effective in tinnitus therapy in individuals with hearing (Andersson et al., 2005; Handscomb, 2006). Second, one might consider an implant electrode configuration that gives barely suprathreshold stimulation through the night to reduce the awareness of tinnitus.

As with hearing aids, optimizing a cochlear implant for tinnitus may involve programming that reduces speech discrimination abilities. The tinnitus program should therefore be addition to the program that is in general use of the cochlear implant (speech communication).

There are two areas of interest where the existing literature is deficient. The first is consideration of the time course of tinnitus inhibition associated with cochlear implant use, about which there is little or no mention in the literature. This is potentially of some interest, as it may shed light on the mechanism by which tinnitus benefit is achieved. If the benefit is immediate one might consider that masking of the tinnitus by the new auditory information is occurring. If, however, the tinnitus suppression occurs over time, then some process of plastic reorganization of the auditory system following implant use can be inferred. These mechanisms are not mutually exclusive, and a longitudinal study would not resolve this completely, but might shed some light on this matter.

The second area is that of children. The existing literature relates to adults, and there is minimal information regarding children with cochlear implants and tinnitus. This is anomalous, as hearing impaired children are known to have prevalent and occasionally severe tinnitus (see Baguley and McFerran, 2002 for review), and the response of

that tinnitus to cochlear implantation would be of some interest, both clinically and scientifically.

New developments

Binaural cochlear implants

In a study by Summerfield et al. (2006) of self-reported benefits from successive cochlear implantation in post-lingually deafened adults, receipt of a second implant led to significant improvements in self-reported abilities in spatial hearing, quality of hearing and in speech perception, but, counter-intuitively, to non-significant changes in quality of life. The essential aim of the study was to determine the incremental benefit (or otherwise) of a second implant. The study had 24 adult participants who were implanted with Nucleus CI24 devices. The participants were randomized either to receive a second implant immediately or to wait 12 months; this latter group acting as a control for emerging benefits of the second device. Multivariate analysis indicated that any improvement in quality of life associated with improved auditory abilities was offset by negative changes associated with worsening of their tinnitus. Of 16 patients with pre-operative tinnitus, 7 reported a worsening (44%), and of 8 patients who did not report tinnitus pre-operatively, 4 (50%) reported that the second implant had induced tinnitus. While the incidences of tinnitus are higher than those generally reported for unilateral implantation (see Table 2) they are not statistically significantly different from normal (Summerfield et al., 2006). Worsened tinnitus following sequential binaural implantation may therefore be sufficient to offset other benefits following surgery.

Functional imaging and cochlear implants

Mirz et al. (2002) used positron emission tomography (PET) to demonstrate the suppressive effect of a cochlear implant in a patient with distressing tinnitus. The use of the cochlear implants not only reduced signs of tinnitus-related activity in primary auditory and associate cortices, but also in areas of the CNS associated with emotion

(limbic system) and attention (dorsolateral prefrontal cortices). PET in three patients (Osaki et al., 2005) in whom there was a marked residual inhibitory effect of cochlear implant use on tinnitus, showed that the right anterior middle and superior temporal gyri (Brodmann areas 21 and 38) were activated during residual inhibition after device use, whereas the right cerebellum was activated during tinnitus perception in the tinnitus patients. Such residual inhibition of tinnitus with cochlear implant use is common (Kim et al., 1995), but may be fleeting (Souliere et al., 1992). The authors concluded that tinnitus, and the residual inhibition of the tinnitus, are associated with central processes of auditory higher order processing, memory and attention. This hypothesis requires significant further research before conclusions can be drawn.

Unilateral SNHL and tinnitus

Idiopathic unilateral sudden SNHL has an incidence of 2–20/100,000 adults per year (Byl, 1984), leading to estimates of 2835–9540 cases per year in the UK alone (Baguley et al., 2006). The hearing loss does not recover in more than 60% of cases in spite of therapy, mainly because the cause and pathogenesis of sudden deafness is unknown (Merchant et al., 2005).

When hearing loss remains severe, tinnitus in the same ear may be disabling as shown by Chiossoine-Kerdel et al. (2000) using the THI (Newman et al., 1996). The same authors also demonstrated a significant hearing handicap in the majority (86%) of these unilaterally affected patients when assessed with the Hearing Handicap Inventory for Adults (Newman et al., 1990). Therefore, tinnitus consecutive to sudden deafness with poor recovery remains a therapeutic challenge (Andersson et al., 2005). Contralateral routing of signal (CROS) and bone-anchored hearing aids (BAHA) can be utilized in auditory rehabilitation, with varying degrees of success (Baguley et al., 2006), but little or nothing can be offered for relief of the tinnitus.

A cochlear implant on the affected side may benefit and not only reduce the hearing handicap

but it may also provide relief for the tinnitus. The application of a cochlear implant to such individuals has so far only been reported in a conference report where Van de Heyning et al. (2006) described a series of 10 patients with a unilateral profound SNHL, associated with “incapacitating and refractive tinnitus” and with normal hearing in the contralateral ear. These individuals were implanted with the Medel Combi 40+ device. On individuals whose tinnitus could be reduced by at least 50% by electrical promontory stimulation were included in the study. Statistically significant improvements in measures of tinnitus loudness (visual analog scale) and impact (Tinnitus Questionnaire, Hallam, 1996) were achieved in all these individuals and all were reported to have used the device all their waking hours for the 12-month duration of the study. In a further report from the same group, Vermeire et al. (2006) describe 18 similar patients (probably including those from the initial report). An additional inclusion criteria described is a >50% inhibition of the tinnitus by electrical promontory stimulation. Programming strategies and outcome measures are not described, but the authors stated “there was no conflict between the hearing with the CI and the hearing in the opposite ear”.

It has been reported that it is possible to integrate regular hearing with cochlear implant stimulation (Dunn et al., 2005) though such auditory fusion may not be possible in all individuals. Optimizing the device for tinnitus inhibition might however involve non-speech related stimulation, and an approach such as the pulse train stimulation trialed by Rubinstein et al. (2003) becomes an option. The development of modified electrode arrays, which aim to preserve low-frequency acoustic hearing and allow mid, and high-frequency electrical stimulation (Gantz and Turner, 2004; Gantz et al., 2006; James et al., 2006; Briggs et al., 2006, for example) may offer some benefit for such patients, many of whom experience troublesome tinnitus.

Soussi and Otto (1994) studied 10 patients who had received an auditory brainstem implant (ABI) following removal of a vestibular schwannoma in patients with neurofibromatosis type 2. Of these, seven used their implant daily, and six of these

“reported noticeable tinnitus reduction” — this represents 86% of the daily user group. This finding is of some potential interest, as the dorsal cochlear nucleus (DCN) (Kuroki and Møller, 1995; Kaltenbach, 2006; Shepherd and McCreery, 2006) has been implicated in tinnitus perception. The electrode array of the ABI is inserted into the lateral recess of the fourth ventricle and placed over the surface of the ventral and dorsal cochlear nuclei (Kuroki and Møller, 1995; Fayad et al, 2006; Shepherd and McCreery, 2006). Progress toward a midbrain implant is also evident (Lenarz et al., 2006; Colletti et al., 2007) and provides further opportunity for the investigation of the possibility of using electrical stimulation of the central auditory system in controlling tinnitus.

Conclusions

This paper has reviewed current observational evidence regarding the effects of cochlear implants on tinnitus. The current literature supports the clinical observation that cochlear implants have a marked suppressive effect on tinnitus in most cochlear implant users. The situation may be different for binaural cochlear implants where auditory benefits of a second implant may be offset by an exacerbation of tinnitus in some patients. Cochlear and brainstem implants can also seem to provide reduction of tinnitus but the experience of such implants is much smaller than that of cochlear implants.

Acknowledgment

This paper was written while David Baguley was a Raine Visiting Professor at the Ear Sciences Institute, University of Western Australia. The support of the Raine Foundation, of Phonak Pty, of the British Tinnitus Association and of Deafness Research UK is gratefully acknowledged.

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CHAPTER 34

Transcranial magnetic stimulation (TMS) for treatment of chronic tinnitus: clinical effects

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Abstract: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method used to induce electrical current in the brain through impulses of strong magnetic fields applied externally. The technique can relieve tinnitus by modulating the excitability of neurons in the auditory cortex to decrease the hyperexcitability that is associated with generating the neural activity that causes some form of tinnitus. This chapter will review clinical studies using rTMS for the treatment of tinnitus.

Keywords: tinnitus; transcranial magnetic stimulation; neuroplasticity; functional imaging; neuronavigation; auditory cortex

Transcranial magnetic stimulation

In 1985 Barker and colleagues showed that it was possible to depolarize neurons in the brain using external magnetic stimulation (Barker et al., 1985). Transcranial magnetic stimulation (TMS) involves applying strong impulses of magnetic fields with a duration of 100–300 µs and a strength of 1.5–2.0 T. Taking advantage of the fact that magnetic fields pass largely undistorted through the scalp and skull, repetitive TMS (rTMS) induces an electric current in the brain that can cause neuronal depolarization in the cortex of humans (Bohning et al., 2000). TMS is much less painful than the transcranial electrical stimulation (TES). For TMS, a brief (100–300 µs) impulse of a strong electrical current in the wires of a coil generates

impulses of magnetic field. The lines of magnetic flux are oriented perpendicularly to the plane of the coil (Fig. 1). The electric current that is induced perpendicularly to the magnetic field can depolarize cells in the underlying brain area.

Magnetic coils of different shapes are in use. Round coils are relatively powerful. The eight-shaped coils generate more focal stimulation with a maximal current at the intersection of the two round parts (Hallett, 2000). Due to the rapid decline of the magnetic field with increasing distance from the coil, effective stimulation is limited to superficial cortical areas. When used for the suppression of tinnitus, a single magnetic impulse does not produce long-lasting effects. Application of multiple impulses, known as rTMS, can have effects that outlast the stimulation. Depending on stimulation parameters, rTMS can cause excitation or inhibition. Low frequency (≤ 1 Hz) rTMS has been repeatedly shown to decrease cortical excitability (Chen et al., 1997; Hoffman and

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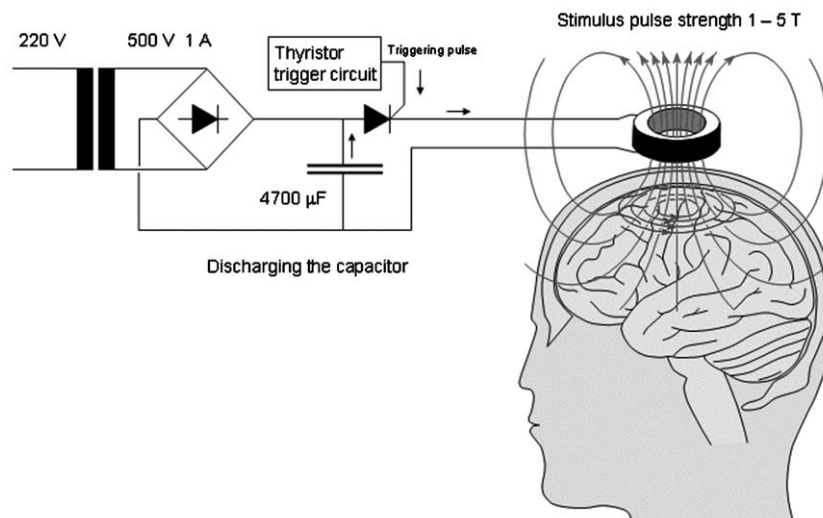


Fig. 1. The principle of TMS with symbolized spread of magnetic fields perpendicular to the coil windings (Adapted with permission from Jaako Malmivuo and Robert Plonsey: *Bioelectromagnetism — Principles and Applications of Bioelectric and Biomagnetic Fields*, Oxford University Press, New York, 1995). (See Color Plate 34.1 in color plate section.)

Cavus, 2002), while high-frequency (5–20 Hz) rTMS increases the excitability of cortical neurons (Pascual-Leone et al., 1994). This is similar to the effect of direct electrical stimulation as demonstrated in animal studies (Post and Keck, 2001; Hoffman and Cavus, 2002). It was assumed that the effect of low frequency rTMS might be similar to long-term depression (LTD), which diminish the efficiency of intercellular connections, whereas high frequency rTMS might generate long-term potentiation (LTP) (Wang et al., 1996). In addition, rTMS can block or inhibit specific functions for brief periods after the stimulation, thus creating a similar effect as a transient functional lesion in the immediate post-stimulation period (Walsh and Rushworth, 1999). The effects of rTMS can outlast the time of stimulation, and the technique is used in the therapy of patients with different kinds of cortical dysfunction (Hallett, 2000).

Rationale for the use of rTMS in treatment of tinnitus

There is increasing evidence that expression of neural plasticity is involved in tinnitus (Møller, 2001, 2003) (see Chapter 3). In particular, many

forms of chronic tinnitus are auditory phantom perceptions (Jastreboff, 1990) that might be a result of maladaptive attempts at cortical reorganization due to distorted sensory input (Møller, 2000). Re-organization may occur at several levels of the ascending auditory pathways and re-direction of auditory information (Chapter 3) may be involved in generating the abnormal neural activity that causes tinnitus and other abnormalities that often accompany severe tinnitus such as hyperacusis (Chapters 1 and 15), depression and phonophobia (Chapter 20). Signs of re-organization of the auditory cerebral cortex have been shown in magnetoencephalographic (MEG) studies. Some such studies have showed indications of a shift in the tonotopic map of the auditory cortex contralateral to the side to which the tinnitus is referred (Mühlnickel et al., 1998). The results of positron emission tomography (PET) have shown signs of an abnormal asymmetry in the auditory cortices of some individuals with tinnitus indicating higher levels of spontaneous activity on the left side, independent on the side to which the tinnitus is referred (Arnold et al., 1996; Kleinjung et al., 2005; Langguth et al., 2006c). Other studies revealed changes in the middle temporal and temporoparietal regions as well as abnormal

activation of frontal and limbic areas (Lockwood et al., 1998; Giraud et al., 1999; Mirz et al., 2000; Johnsrude et al., 2002).

Since rTMS has the ability to modulate cortical activity focally, it seems likely to assume that application of rTMS to cortical auditory areas can alleviate tinnitus. Promising results have been obtained by the use of rTMS in the treatment of other disorders which have been associated with abnormal cortical activity such as auditory hallucinations (Hoffman et al., 2003, 2005; Langguth et al., 2006d), writer's cramp (Siebner et al., 1999) and some obsessive compulsive disorders (Mantovani et al., 2006).

It has been shown that trains of high-frequency rTMS (10–20 Hz) can induce an immediate, short-lasting interruption of tinnitus perception, whereas repeated stimulations with low-frequency (1 Hz) rTMS on several consecutive days can have a lasting beneficial effect on tinnitus and thus represent a potential therapeutic method.

The designs and results of recent studies regarding the effect of rTMS on tinnitus are summarized in Table 1 (for review see Langguth et al., 2006b; Londero et al., 2006b; Pridmore et al., 2006).

High frequency rTMS

The hypothesis that the temporoparietal cortex plays a major role in the pathophysiology of some forms of tinnitus is supported by the results of studies using high frequency rTMS.

In a study where high-frequency rTMS (10 Hz) was applied to eight scalp and four control positions in 14 individuals with chronic tinnitus (2 left-sided, 12 bilateral), a significant transient reduction of tinnitus was only observed when stimulation was administered to the left temporoparietal cortex (Plewnia et al., 2003) and suppression of the tinnitus occurred in 57% of the participants. In a larger series of 114 individuals with unilateral tinnitus, De Ridder et al. (2005) applied rTMS at frequencies between 1 and 20 Hz over the auditory cortex contralateral to the site of the tinnitus. Twenty-eight percent of the participants reported improvement (20–79% reduction in

subjective tinnitus perception) and 25% reported suppression (80–100% reduction in subjective tinnitus perception). The amount of tinnitus suppression was correlated positively with stimulation frequency and negatively with tinnitus duration, indicating the potential of TMS as a diagnostic tool for differentiating different forms of chronic tinnitus. These findings were confirmed in two other studies, Fregni et al. (2006) and Folmer et al. (2006) showing suppression of tinnitus in 42% and 40% of the participants. In addition, one of the studies (Fregni et al., 2006) found that the participants in their study who had significant reduction after rTMS also showed good response to anodal transcranial electrical current stimulation (dTCS).

Low frequency rTMS

Based on the success of 1 Hz rTMS in treating other conditions which appeared to be associated with increased cortical activity, low frequency rTMS has been proposed as a potential treatment for patients with disabling tinnitus (Eichhammer et al., 2003; Langguth et al., 2003). In these studies PET imaging and a neuronavigational system were used to focus the magnetic field on the site of maximum activation of the auditory cortex.

Stimulation with 2000 magnetic impulses per day at an intensity of 110% of the motor threshold (MT) was used in three individuals with chronic tinnitus (2 left-sided, 1 bilateral) on five consecutive days in a sham-controlled cross-over design (Fig. 2). Active and sham treatments were separated by one week. Two patients reported improvement of the tinnitus by an average of 10.5 points on the tinnitus questionnaire (Goebel and Hiller, 1994), three days after active stimulation but not after sham treatment. Treatment success sustained for the following week. Patient 3 had moderate improvement during both sham and active TMS. As the first results were encouraging, the same authors (Kleinjung et al., 2005) conducted a sham-controlled TMS study on 14 patients using the identical study design. After five days of rTMS, a highly significant improvement of the tinnitus score was found whereas

Table 1. Clinical effects of high- and low-frequency rTMS in tinnitus patients^a

Authors	Number of patients, tinnitus laterality	Cortical target	Stimulation frequency, intensity	Sham control	Number and duration of trains	Results
(a) High-frequency rTMS in tinnitus patients						
Plewnia et al. (2003)	14 (12 bilateral, 2 left-sided)	Various scalp positions according to 10–20 EEG system	10 Hz, 120% MT ^b	Control positions	1 train of 3 s (30 p.) ^b	8 responders for left temporal/temporoparietal stimulation
Fregni et al. (2006)	7 (bilateral)	Left temporoparietal and mesial parietal areas, according to 10–20 EEG system	10 Hz, 120% MT	Sham coil	1 train of 3 s (30 p.)	3 responders for active stimulation of left temporoparietal target
Folmer et al. (2006)	15 (8 right-sided, 7 left-sided)	Left and right temporal cortex, according to 10–20 EEG system	10 Hz, 100% MT	Sham coil	5 trains of 3 s (150 p.) during 5 min	6 responders for active stimulation (5 left temporal cortex, 1 right temporal cortex), 2 responders for sham TMS
De Ridder et al. (2005)	114 (106 unilateral, 8 bilateral)	Auditory cortex contralateral to tinnitus site	1–20 Hz, 90% MT	Control positions, coil perpendicular to the skull	1 train of 10–66 s (200 p.)	28 good and 32 partial suppression to active rTMS, 38 responders to sham rTMS; highest amount of tinnitus suppression for tinnitus duration up to 3 years at 20 Hz, in tinnitus for more than 3 years only partial suppression
Londero et al. (2006a)	13 (10 left-sided, 3 right-sided)	Various positions (target areas determined by fMRI, as well as adjacent non-specific cortical areas)	10 Hz, 120% MT	Control positions	1 train of 3 s (30 p.)	1 responder for non-specific stimulation site

(b) Low-frequency rTMS in tinnitus patients^a

Kleinjung et al. (2005)	14 (2 bilateral, 6 bilateral left-predominant, 6 bilateral right-predominant)	Area of maximum tinnitus related PET activation (12 left and 2 right auditory cortex), neuronavigational system	1 Hz, 110% MT ^b	Sham coil	5 trains of 33 min (2000 p.) ^b on 5 following days	8 responders for active rTMS, 5 non-responders, 1 worsened patient, clinical improvement remained stable over a 6 months follow-up
Londero et al. (2006a)	13 (10 left-sided, 3 right-sided)	Auditory cortex contralateral to tinnitus: area of maximal fMRI activation	1 Hz, 120% MT	(Occipital) control position	1 train of 20 min (1200 p.)	5 responders for the auditory target stimulation (effects remained from 2 to 10 days), 1 responder for the control position
Plewnia et al. (2007a)	9 (8 bilateral, 1 right-sided)	Area of maximum tinnitus related PET activation, neuronavigational system	1 Hz, 120% MT	Non-specific (occipital) control position	3 trains of 5, 15, 30 min (300, 900, 1800 p.) with intertrain intervals of 30 min	6 responders for active rTMS with reduced tinnitus perception up to 30 min. Increasing amount of rTMS pulses causes more pronounced suppression of tinnitus, long tinnitus duration is correlated with less effect
Langguth et al. (2006a)	28 (13 bilateral, 9 left-sided, 6 right-sided)	Left primary auditory cortex according to 10–20 EEG system	1 Hz, 110% MT	None	10 trains of 33 min (2000 p.) on 10 subsequent working days	Significant change in tinnitus score until end of follow-up (13 weeks)
Plewnia et al. (2007b)	6 (all bilateral)	Area of maximum tinnitus-related PET activation, neuronavigational system	1 Hz, 120% MT	Non-specific (occipital) control position	20 trains of 30 min (1800 p.) on 20 subsequent working days	5 responders for active rTMS, 2 weeks after treatment tinnitus perception returned to baseline
Kleinjung et al. (2007)	45 (30 bilateral, 8 left-sided, 7 right-sided)	Left primary auditory cortex, neuronavigational system	1 Hz, 110% MT	None	10 trains of 33 min (2000 p.) on 10 subsequent working days	18 responders, they were characterized by shorter tinnitus duration and less hearing impairment

^aCase series of less than five patients were excluded from the table, but they are cited in the text.

^bMT: motor threshold, p.: pulses.



Fig. 2. Laboratory setting: rTMS application in a tinnitus patient. The neuronavigational system (1) is used to determine the optimal position of the stimulation coil (2) in relation to the patient's skull. (See Color Plate 34.2 in color plate section.)

the sham treatment did not show any significant changes. At 6 months after treatment, eight patients reported a sustained reduction in tinnitus perception reflected by an average reduction of the tinnitus score by 12.4 points in these eight patients. However, there was a high interindividual variability of the treatment effect, which led the authors into a new study that focussed on possible predictors for treatment response (Kleinjung et al., 2007). The main finding was a significant relationship between tinnitus duration and benefit from treatment. In accordance to other studies (De Ridder et al., 2005, 2006; Plewnia et al., 2007a), shorter tinnitus duration was related to a better treatment outcome. Normal hearing has been identified as a second predictor for favorable treatment outcome.

Another study (Langguth et al., 2007a) investigated whether neuroimaging guided coil localization is a necessary condition for treatment success using low frequency rTMS in tinnitus patients. An easily applicable coil positioning method based

on the international 10–20 EEG system has been developed to target the left auditory cortex. The use of this coil positioning method improved the outcome of the rTMS, achieving significant reduction of tinnitus severity after 10 sessions of 1 Hz rTMS. Interestingly a case study, which investigated systematically the optimal coil position for tinnitus reduction over the temporal region, resulted in a very similar position, but on the right side (Fierro et al., 2006).

Several other studies using low frequency rTMS in tinnitus patients offered new approaches in the assessment of tinnitus-related activity. Two studies by Plewnia et al. (2007a, b) investigated tinnitus patients, which responded to an intravenous bolus of lidocaine. By using [^{15}O]H $_2$ O PET before and after lidocaine injection they identified changes in neuronal activity in the left middle and inferior temporal (BA 37), in the right temporoparietal cortex (BA 39) and in the posterior cingulum. Then single sessions of 5, 15 and 30 min low frequency rTMS were performed in a

sham-controlled design with the coil localized over the brain areas where lidocaine exerted maximal effects. Tinnitus reduction occurred in six out of eight subjects and lasted up to 30 min. There was a high variability of treatment results with better effects after longer duration of the stimulation, and in patients with shorter tinnitus duration. In a second study the same authors (Plewnia et al., 2007b) extended the effects of single sessions of 1 Hz rTMS into a therapeutic application by using a sham-controlled cross-over design with 2×2 weeks of rTMS applied over the area of maximum lidocaine-related activity change as determined by [^{15}O]H $_2$ O PET. They reported moderate, but significant effects after active stimulation with high interindividual variability. However, 2 weeks after the last session treatment effects were no longer detectable.

Another recent study (Londero et al., 2006a) compared high- and low-frequency rTMS in 13 patients. The target for stimulation was determined by functional magnetic resonance imaging (fMRI). Auditory stimulation with sounds similar to the individual subjective tinnitus sensation resulted in activation of the auditory cortex contralateral to the perceived tinnitus. Single short high-frequency rTMS trains over this area resulted only in one patient in any reliable tinnitus suppression. On the other hand after one long single train of low-frequency rTMS, the majority of investigated patients reported a reduction of their tinnitus. The duration of effects was highly variable, lasting up to 10 days.

Further support for beneficial therapeutic effects of low frequency rTMS comes from a recent case study (Richter et al., 2006). 1 Hz rTMS was applied on five consecutive days (1800 pulses/day) to a patient with a 30-year history of bilateral tinnitus. The coil was navigated to the area of increased cortical activation as identified by fluorodeoxyglucose positron emission tomography (FDG PET)-CT (right primary auditory cortex). The patient reported beneficial changes in tinnitus perception persisting up to 4 weeks, and there was a statistically significant improvement in objective measures of attention and vigilance. Interestingly a PET study performed two days after rTMS treatment did not demonstrate any relevant changes as

compared to the baseline scan. The authors suggest that the persistent changes of neural activity after rTMS treatment might represent a predictor for the return of tinnitus perception.

Conclusion

The results of an increasing number of published results of studies using rTMS indicate that treatment of tinnitus with this method is promising for patients with certain forms of tinnitus. However further clinical and neurobiological research is needed before rTMS can be considered to be a practical treatment option for routine use. Replication of the published results must be done in multicenter trials with many patients and longer follow-up periods in order to estimate the efficacy of rTMS for treatment of tinnitus. Further research is needed to define subgroups of patients that benefit most from rTMS and to optimize stimulation protocols.

Abbreviations

FDG PET	fluorodeoxyglucose positron emission tomography
fMRI	functional magnetic resonance imaging
LTD	long-term depression
LTP	long-term potentiation
MEG	magnetoencephalography
MT	motor threshold
PET	positron emission tomography
TES	transcranial electrical stimulation
TMS	transcranial magnetic stimulation
rTMS	repetitive transcranial magnetic stimulation

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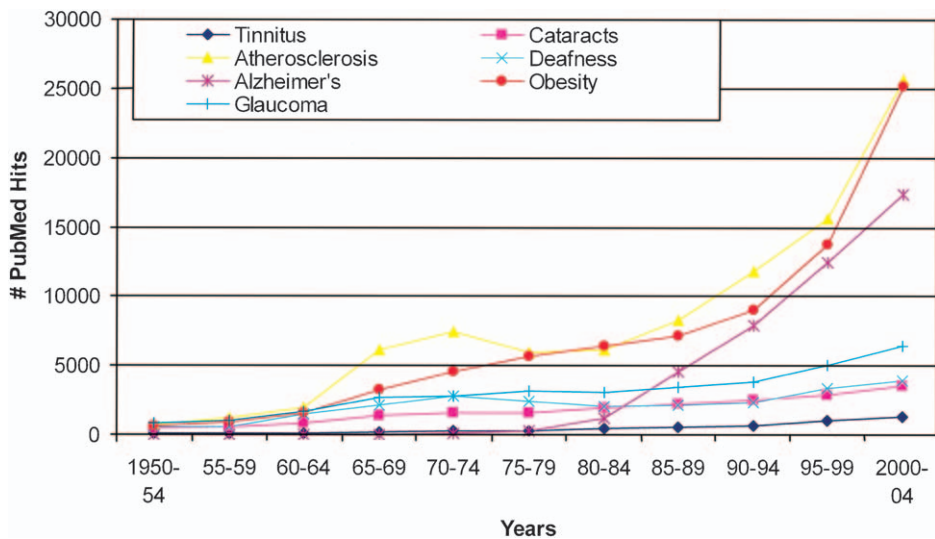


Plate 13.1. Number of PubMed hits as a function of year for the search term “tinnitus” as well as a variety of other sensory conditions. Even though tinnitus is much more common in the general population than either “glaucoma” or “cataracts”, the level of research produced on tinnitus is substantially less. Also surprising is the relatively flat research productivity on “deafness”. (For B/W version, see page 148 in the volume.)

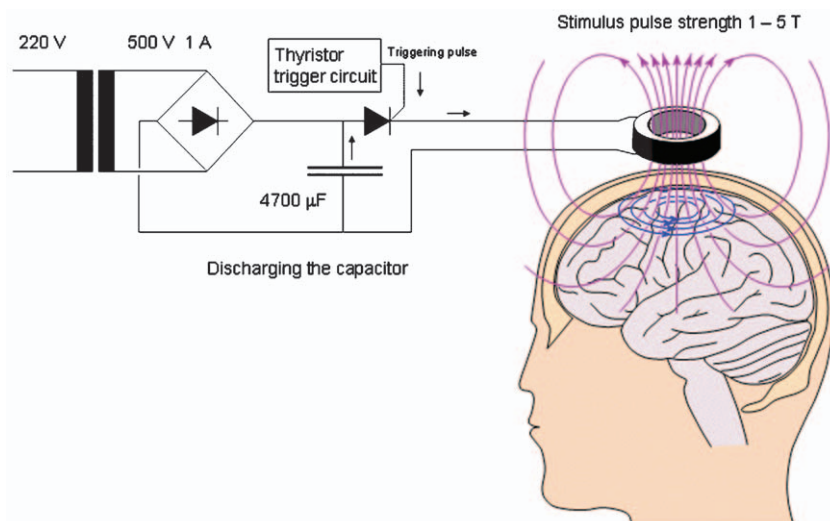


Plate 34.1. The principle of TMS with symbolized spread of magnetic fields perpendicular to the coil windings (Adapted with permission from Jaako Malmivuo and Robert Plonsey: Bioelectromagnetism — Principles and Applications of Bioelectric and Bio-magnetic Fields, Oxford University Press, New York, 1995). (For B/W version, see page 360 in the volume.)



Plate 34.2. Laboratory setting: rTMS application in a tinnitus patient. The neuronavigational system (1) is used to determine the optimal position of the stimulation coil (2) in relation to the patient's skull. (For B/W version, see page 364 in the volume.)

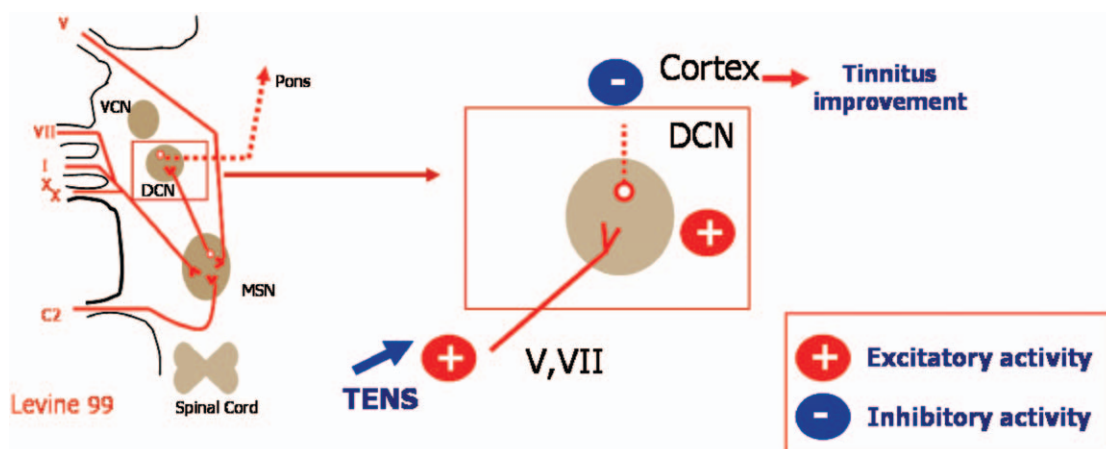


Plate 37.1. Representation of the pathways involved in somatic tinnitus modulation. We show the possible place where the trans-electrical nerve stimulation could act and reduce tinnitus intensity. The effect of TENS in the somatic tinnitus could restore the dorsal cochlear nucleus (DCN) inhibition through the electrical stimulation of the somatic pathway. (For B/W version, see page 390 in the volume.)

CHAPTER 35

TMS for treatment of chronic tinnitus — neurobiological effects

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Abstract: Results of neurophysiological and neuroimaging studies suggest that some forms of chronic tinnitus can be regarded to be “hyperexcitability syndromes”, caused by abnormal focal brain activity. Low frequency repetitive magnetic stimulation (rTMS) is an efficient method to selectively reduce the abnormally increased activity in distinct cortical areas. An increasing amount of clinical data suggest that low frequency rTMS might be an effective therapy that is directed at the cause of some forms of chronic tinnitus. To further explore the underlying neurobiological mechanisms we investigated the effect of rTMS on cortical excitability in healthy human subjects using the protocol, which has been successfully used for the treatment of tinnitus. We determined different parameters of motor cortex excitability (resting motor threshold, RMT; active motor threshold, AMT; short intracortical inhibition, ICI; short intracortical facilitation, ICF; and the duration of the cortical silent period, CSP) before and after 5 days of low frequency rTMS (2000 stimuli/day at 110% of RMT) over the left auditory cortex. Five sessions of low frequency rTMS resulted in a significant prolongation of the CSP. All other signs of cortical excitability that we studied remained unchanged. These findings suggest, that low frequency rTMS may evoke long-term depression (LTD)-like effects resulting in enhancement of subcortical inhibition.

Keywords: tinnitus; low frequency transcranial magnetic stimulation; neuroplasticity; subcortical inhibition; thalamic gating; GABA_B

Introduction

With the advent of modern neurophysiological and imaging tools a new conceptual framework evolved pointing to abnormal functioning of the central nervous system as the decisive neurobiological basis of chronic tinnitus (Jastreboff, 1990; Möller, 2003). Several different studies have provided evidence that support this hypothesis. Thus, neuroimaging studies of individuals with tinnitus

have shown signs of enhanced activation of the central auditory system (Arnold et al., 1996; Giraud et al., 1999; Mirz et al., 1999). Studies using magnetic source imaging have shown evidence of abnormalities in the tonotopic maps of the auditory cortex (Muhlnickel et al., 1998; Weisz et al., 2005). Recent studies have emphasized the relevance of dysfunctional thalamocortical processing in the pathogenesis of tinnitus (Llinas et al., 1999; Schwarz et al., 2000; Reyes et al., 2002; Eichhammer et al., 2004). MRI studies have demonstrated structural changes at the thalamic level in individuals with tinnitus thus indicating expression of structural

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plasticity (Muhlau et al., 2006). The regions of the CNS that have been shown to be structurally or functionally altered in individuals with tinnitus may represent potential treatment targets for brain stimulation techniques such as electrical stimulation or repetitive transcranial magnetic stimulation (rTMS) (see Chapters 34 and 35). Applied in a low frequency range, rTMS reduces brain activity in specific regions that are directly stimulated (Chen et al., 1997). Activity changes also occur in remote areas that are functionally connected to the direct stimulated areas (Siebner et al., 2003). Evidence that rTMS causes expression of neural plasticity in cortical circuits including thalamocortical networks has been presented (Wang et al., 1996; May et al., 2007). It is assumed that these effects of rTMS are responsible for the reduction of auditory hallucinations in patients with schizophrenia (Hoffman et al., 2003; Jandl et al., 2006). In a similar study we showed that low frequency rTMS applied over the hyperactive auditory cortex might reduce the severity of tinnitus (Eichhammer et al., 2003; Kleinjung et al., 2005). The placement of the stimulating coil was guided by PET- and MRI scans using neuronavigation in a sham controlled crossover designed study. The benefit from this treatment remained stable in 6 of 14 treated patients until the end of the observation period (6 month) (Kleinjung et al., 2005) suggesting involvement of neuroplastic processes (Langguth et al., 2003; May et al., 2007). Preliminary imaging data suggest that treatment effects depend on the level of activity in the stimulated auditory cortex (Langguth et al., 2006a) and in frontal brain areas (Plewnia et al., 2007).

The objective of the present study was to evaluate the effects of 1 Hz rTMS over the auditory cortex on objective measures of cortical excitability. For this purpose we used transcranial magnetic stimulation (TMS) to assess several measures of motor cortical excitability before and after five sessions of 1 Hz rTMS over the left auditory cortex in healthy controls. We used the similar measures of cortical excitability assessed by TMS as (a) have been used to assess effects of rTMS on motor cortex excitability (Gerschlagel et al., 2001; Siebner et al., 2003; Siebner et al., 2004; Khedr et al., 2007), (b) have been shown to be sensitive for detecting

practice-dependent and deafferentation-induced plasticity of the human cortex (Ziemann et al., 1998, 2001), and (c) have provided new insights into the mechanisms of cortical plasticity (Chen et al., 1998). It is well-known that there are extensive functional connections between the auditory cortex and the motor cortex (Graziano et al., 1999; Speer et al., 2003) and these connections may be the physiological basis for the detection of changes of auditory processing by measuring motor cortex excitability (Langguth et al., 2003, 2005; Aziz-Zadeh et al., 2004; Kuhn et al., 2004).

Materials and methods

Selection criteria

A group of 36 healthy volunteers without tinnitus (27 female, 9 male; mean age, 24.8 years) was divided into two to age and gender matched groups. One group was to receive active rTMS and the other group was to receive sham rTMS. Written informed consent was obtained from all participants. All participants were subjected to a neurological and psychiatric examination to ensure that the participants did not suffer from any neurological or psychiatric disease. The study was approved by the local ethics committee.

All prospective participants had standard otologic examination including examination of the ear to exclude tympanic membrane defects and middle ear effusion. Normal middle ear status and normal hearing were also requirement for inclusion and tympanometry and recording of acoustic middle ear reflexes were done. "Normal hearing" was defined as pure tone threshold equal or better than 20 dB HL at any frequency between 0.25 and 8 kHz. All audiological measurements were repeated after completion of the stimulation.

rTMS stimulation

A neuronavigation system normally used in neurosurgery (Gumprecht et al., 1999) and further developed and adopted for TMS (Vector-Vision, BrainLab AG, München-Heimstetten, Germany) was used in the present study for administration of

rTMS. The system used in this study allows real time stereotactic monitoring of the location of the coil in relation to the cortex (Eichhammer et al., 2003) (see Chapter 34). Based on individual T1-weighted MRI-scans, the left superior temporal gyrus (Brodmann area 41/42), corresponding to the primary auditory cortex, was the target for rTMS (Langguth et al., 2006b).

A Magstim stimulator (Magstim Co., Whiteland, Dyfed, UK) using a figure-of-eight coil was used to administer the rTMS. Stimulation was applied once daily for 5 days. Two thousand stimuli at a frequency of 1 Hz and at a strength of 110% of the resting motor threshold (RMT) were applied per session. A special sham-coil system was used for the sham stimulation (Magstim Co., Whiteland, Dyfed, UK). This coil does not induce a magnetic field, but evokes an acoustic artifact that is similar to sound generated by the active coil.

Measurement of cortical excitability

Different signs of cortical excitability (RMT; active motor threshold, AMT; intracortical inhibition, ICI; intracortical facilitation, ICF; cortical silent period, CSP) were assessed before and after administration of active and sham rTMS (Fig. 1).

Motor-evoked potentials (MEP) of the abductor digiti minimi (ADM) muscle of the right hand were recorded with surface electrodes, using a conventional EMG machine (Medelec, UK) with band-pass of 20 Hz–10 kHz. The signal was digitized at a sampling rate of 5 kHz and transferred to a laboratory computer for off-line analysis. TMS

was performed using a Bistim module, which was connected to two Magstim 200 stimulators (Magstim Co., Whiteland, Dyfed, UK). The figure-of-eight coil (outer diameter of each wing 90 mm) was held with the junction of the two wings tangential to the skull and the handle pointing backwards and at an angle of approximately 45° from the midline. Since the induced current in the brain is directed approximately perpendicular to a line through the central sulcus it is assumed to be optimal for activating the corticospinal pathways transsynaptically. The optimal coil position over the left motor cortex for eliciting a MEP in the ADM was determined. RMT was defined as the lowest stimulus intensity that evoked a MEP of at least 50 μ V peak to peak in the resting ADM in at least four out of eight consecutive trials and AMT as the lowest stimulus intensity that evoked at least 250 μ V during isometric contraction of the ADM at about 20% of maximum voluntary contraction in at least four out of eight consecutive trials. A constant level of voluntary contraction was maintained by audiovisual feedback of the EMG activity. CSP duration was defined as the interval between the end of the MEP and the first reappearance of voluntary EMG activity. Intracortical excitability was measured in the resting ADM using a paired-pulse paradigm (Kujirai et al., 1993) consisting of a subthreshold conditioning pulse followed by a suprathreshold test pulse. The intensity of the first stimulus was set to 90% AMT and the intensity of the second stimulus was adjusted to produce an unconditioned MEP of approximately 1 mV. Inter-stimulus intervals (ISIs) of 2–8, 10, 15, and 20 ms were used; each

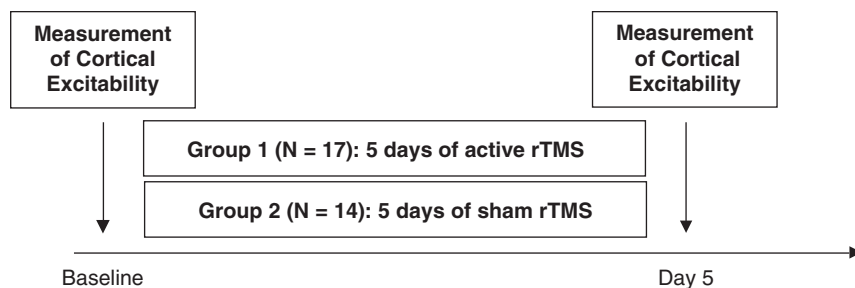


Fig. 1. Research design: different parameters of cortical excitability were assessed before and after 5 days of rTMS over the left auditory cortex.

interval was tested at least ten times in a random order. The interval between the applications of the pairs of stimuli was 4 s. The effect of conditioning stimuli on MEP amplitude at each ISI was determined as the ratio of the average amplitude of the conditioned MEP to the average amplitude of the unconditioned test MEP obtained in the same block of trials. Since it was known from previous studies (Kujirai et al., 1993) that the conditioning stimulus has a suppressive effect on the control MEP at short ISIs (2–5 ms) and a facilitatory effect at longer ISIs (7–20 ms), ICI and ICF were calculated across these intervals, respectively.

Statistical analysis

The different measures of cortical excitability were tested separately for the active and for the sham group by using paired *t*-tests. The significance level for all tests was set to $p < 0.05$.

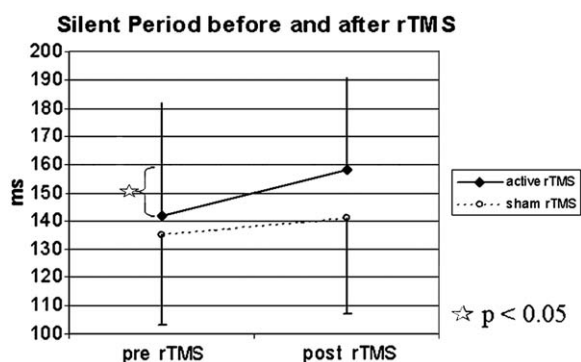


Fig. 2. Cortical silent period (CSP) before and after active and sham rTMS: there was a significant increase of the CSP after active rTMS ($p < 0.05$) but not after sham rTMS.

Results

All participants tolerated the stimulation procedure without any noticeable side effects. Pure tone audiometry did not show any noticeable changes after active or after sham stimulation. Due to technical reasons, excitability measurements could only be obtained in 31 of the 36 participants in the study (26 females, 5 males; 17 active stimulation; 14 sham stimulation). There was a significant prolongation of the CSP after active stimulation ($p = 0.006$), but no significant change after the sham intervention ($p = 0.35$) (Fig. 2). All other tested parameters of cortical excitability (ICI, ICF, RT, AT) were unchanged after active rTMS and sham rTMS. Mean values and standard deviations for the different excitability parameters before and after rTMS are shown in Table 1.

Discussion

The main finding of this study was that low frequency rTMS applied over the auditory cortex according to a stimulation protocol that has been successfully used for the treatment of tinnitus resulted in changes of the CSP in healthy controls. The sham group revealed no noticeable change of the SP. Several aspects of this finding are relevant to understanding of the neurobiological effects of low frequency rTMS.

The results of the present study are in agreement with results obtained by low frequency rTMS over the motor and premotor cortex which showed similar prolongation of the SP in individuals with writer's cramp (Siebner et al., 1999) as well as in

Table 1. Parameters of cortical excitability before and after active and sham rTMS

	Active rTMS			Sham rTMS		
	Pre	Post	<i>p</i>	Pre	Post	<i>p</i>
RT	48.1 ± 9.2	50.9 ± 10.1	0.07	49.3 ± 10.6	51.3 ± 12.2	0.36
AT	31.1 ± 5.3	32.2 ± 7.0	0.47	33.6 ± 10.1	34.1 ± 8.7	0.09
ICI	0.66 ± 0.18	0.62 ± 0.19	0.31	0.71 ± 0.35	0.68 ± 0.32	0.69
ICF	1.56 ± 0.42	1.54 ± 0.34	0.85	1.57 ± 0.61	1.59 ± 0.42	0.34
SP	142 ± 40	158 ± 33	0.006	135 ± 32	141 ± 34	0.35

Notes: RMT, resting motor threshold (in % max. stimulator output); AMT, active motor threshold (in % max. stimulator output); ICI, intracortical inhibition; ICF, intracortical facilitation; CSP, cortical silent period (in ms); all data are indicated as mean ± standard deviation.

healthy controls (Cincotta et al., 2003; Khedr et al., 2004; Doumas et al., 2005; Lang et al., 2006). The results of the present study also lend support for the presence of extensive functional connections between the central auditory system and the motor cortex as has been described previously both anatomical (Graziano et al., 1999) and functional (Speer et al., 2003; Aziz-Zadeh et al., 2004; Kuhn et al., 2004). The observed changes in excitability of the motor cortex after stimulation of the auditory cortex confirms that the effect of rTMS propagates from the directly stimulated cortical area to other brain regions, and thereby having the ability to modulate activity in other neuronal circuits (Paus et al., 2001).

The observed changes in the excitability of cortical regions from low frequency rTMS applied over the auditory cortex might help to understand how the use of rTMS in treatment of patients with tinnitus works. Prolongation of the SP has been shown to reflect increased inhibition within cortical and subcortical structures, including the thalamus (Ziemann et al., 2000; Munchau et al., 2002). A lengthening of the SP has been observed to occur after pharmacologic enhancement of GABA_B transmission by baclofen (Siebner et al., 1998) and tiagabin (Werhahn et al., 1999). Thus, the findings of the present study may indicate that 1 Hz rTMS enhances GABA_B-mediated inhibition. Other studies using neuroimaging have shown evidence that indicates that low frequency rTMS modulates thalamocortical networks (May et al., 2007). The changes these investigators observed after one week of rTMS applied over the temporal cortex in healthy volunteers were interpreted as being caused by expression of neural plasticity at the level of the auditory cortex and the thalamus. These findings in humans are similar to findings in animal studies where direct electrical stimulation of corticothalamic fibers caused inhibition of relay cells mediated by GABAergic neurons in the reticular nucleus (RTN) of the thalamus (Destexhe et al., 1998; Golshani et al., 2001). Virtually all neurons in the RTN are GABAergic and since the neurons in the RTN control neural traffic to and from thalamic nuclei such increased inhibition can influence large parts of the thalamus including the auditory thalamus (MGB) (Tennigkeit et al., 1998;

Steriade, 2001). Thus, in analogy to electrical stimulation low frequency rTMS might reduce cortical excitability by activating inhibitory GABAergic neurons in the RTN.

If low frequency rTMS exerts its clinical effects on tinnitus by modulating thalamocortical circuits through corticothalamic connections to the RTN, the brain area where stimulation has a beneficial effect would not be limited to a small area of the cortex. The hypothesis that 1 Hz rTMS exerts clinical effects by modulating thalamocortical processing is supported by the experience that the beneficial effect seems to be independent of the exact localization of the coil over the temporal cortex.

Investigations in individuals with tinnitus are necessary to clarify whether rTMS induced changes in cortical excitability are related to its beneficial effect effects in treatment of tinnitus.

Abbreviations

ADM	abductor digiti minimi muscle
AMT	active motor threshold
EMG	Electromyography
GABA	Gamma-aminobutyric acid
Hz	Hertz
ICF	intracortical facilitation
ICI	intracortical inhibition
ISI	interstimulus interval
MEP	motor-evoked potentials
RMT	resting motor threshold
rTMS	repetitive transcranial magnetic stimulation
RTN	reticular nucleus of the thalamus
CSP	cortical silent period
TMS	transcranial magnetic stimulation

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CHAPTER 36

Electrical stimulation of auditory and somatosensory cortices for treatment of tinnitus and pain

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Abstract: The efficacy of electrical stimulation of the auditory cortex using extradural implanted electrodes for treatment of tinnitus was studied in 12 patients suffering tinnitus. The effect of similar stimulation of the somatosensory cortex for treatment of neuropathic pain was studied in five patients. It was shown that patients with pure tone type of tinnitus experienced a significant 97% suppression on average while those who had noise type tinnitus only had non-significant 24% suppression. All patients with pain experienced a significant reduction of their pain (using a visual analog scale), and in four out of five it was clinically relevant, i.e., the patient is really helped by it. It is concluded that electrical stimulation of sensory cortices can be effective treatments of severe unilateral tinnitus and unilateral neuropathic pain in selected patients. The results suggest that similar pathophysiological mechanisms underlie some forms of these phantom sensations, and therefore, similar treatment such as electrical stimulation of the respective sensory cortices can suppress tinnitus and pain.

Keywords: auditory; neural plasticity; deafferentation; neurostimulation; pain; tinnitus; auditory cortex; somatosensory cortex

Introduction

There are many similarities between neuropathic pain and tinnitus (Tonndorf, 1987; Möller, 1997, 2000, 2006b) (Chapter 4). Both symptoms are subjective sensations that may over time change in character and quality, and which may be different in different individuals (Chapter 1). Both symptoms can often be masked and modulated by electrical stimulation of the nervous system with a resulting residual inhibition (Chapter 47). Cutting the cochlear nerve often does not improve tinnitus

nor does severing a somatosensory nerve alleviate central neuropathic (physiologic) pain.

Individuals with tinnitus sometimes perceive a normal sound as unpleasant or painful and the tolerance for sounds may be lowered (hyperacusis) (Tonndorf, 1987; Möller, 1997, 2000). Individuals with neuropathic pain often have a stronger than normal reaction to painful stimuli and the reaction is prolonged (hyperpathia) similar to the prolonged worsening of tinnitus and hyperacusis from sound stimulation seen in individuals with tinnitus (Möller, 2006a). The wind-up phenomenon, well known in pain, describes a worsening of pain sensation with repeated stimuli of the same intensity. A similar phenomenon is encountered by individuals with tinnitus who often perceive an increasing

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unpleasant sensation on repeating the same sound (Møller, 1997, 2000). Furthermore, limbic symptoms such as fear, depression, or anxiety as well as a clear stress response are often present both in individuals with phantom pain and tinnitus (Møller, 1997, 2000) (Chapter 1).

These similarities regarding the symptoms of pain and tinnitus suggest a similar pathophysiological mechanism that may underlie both tinnitus and neuropathic pain. Studies in humans have shown indications that reorganization of the topographic maps in the somatosensory and auditory cortex occurs in neuropathic pain and tinnitus respectively (Flor et al., 1995; Muhlnickel et al., 1998) and the amount of pain and tinnitus is related to the degree of reorganization.

Normal development of tonotopy and somatotopy requires sensory input (Woolsey and Wann, 1976; Harrison et al., 1998; Sininger et al., 1999) and abnormal sensory input, whether physiological (Recanzone et al., 1992b, 1993; Gao and Suga, 1998; Weinberger and Bakin, 1998) or pathological (Kaas et al., 1983; Harrison et al., 1998; Dietrich et al., 2001), may induce reorganization of the cerebral cortices in the developing auditory or somatosensory cortex (SSC) and to a lesser degree in the adult cortices (Chapter 3). Direct cortical stimulation can induce reorganization that can modify tonotopic and somatotopic maps (Recanzone et al., 1992a; Suga et al., 2000; Suga and Ma, 2003).

Deprivation of sensory input is a powerful initiator of expression of neural plasticity causing topographic map reorganization in the motor and sensory cerebral cortices (Kaas, 1991; Kral et al., 2000). Short-term and long-term topographic reorganization is governed by different mechanisms: short-term reorganization probably involves change in synaptic efficacy resulting in disinhibition of suppressed GABAergic inputs and potentiation of silent NMDA mediated synapses (Jain et al., 1998), and change in protein synthesis (Sie and Rubel, 1992), while long-term reorganization is mediated by dendritic and axonal sprouting (Kaas, 1991, 1996; Jain et al., 1998). This assumption is largely based on the results of electrophysiological studies, as available morphological data pertaining to cortex reorganization are very limited (Churchill et al., 2004).

The neurobiological, pathophysiological, and clinical analogies between tinnitus and neuropathic pain (Tonndorf, 1987; Jastreboff, 1990; Møller, 1997, 2000, 2006b) suggest that the strategy recently developed for treating tinnitus (De Ridder et al., 2006) may also be useful in treatment of neuropathic pain (see also Chapters 34 and 35). This treatment makes use of functional neuroimaging techniques such as positron emission tomography (PET) scan, functional MRI (fMRI), or magnetic source imaging (MSI) to identify areas of hyperactivity or reorganization and transcranial magnetic stimulation (TMS) to test if the tinnitus can be affected by stimulation of the identified areas of the cortex. If the result of the test is positive, electrodes for chronic electrical stimulation are implanted extradurally over the area of the cortex that showed signs of hyperactivity or reorganization.

In the present study, this technique was used in 12 individuals with tinnitus and 8 individuals with neuropathic (deafferentation) pain using techniques described earlier by implanting electrodes (De Ridder et al., 2004, 2006) over the area of the auditory cortex or SSC that showed signs of reorganization or hyperactivity.

Methods and materials

Tinnitus

Twelve patients, of whom 10 with unilateral tinnitus, were selected for auditory cortex implantation in an attempt to suppress intractable unilateral tinnitus (De Ridder et al., 2006) (Table 1). The results of this study have been published before (De Ridder et al., 2006).

Neuropathic pain

Eight patients (one male, seven females) with intractable neuropathic pain syndromes caused by sensory deprivation were enrolled. They all underwent an fMRI with the SSC as region of interest using tactile stimulation of the area of allodynia/hyperalgesia. Selection criteria for implantation are >50% pain suppression on an fMRI-based

Table 1. Auditory cortex stimulation: individual patient data and outcomes after auditory cortex stimulation for tinnitus

Age/ sex	T side	T duration	T frequency	T dB	VAS	T grade	Hear loss	T noise	TMS suppression	ED supp N	ED supp PT	ID supp N	ID supp PT	VAS postop	IPG	Follow- up (months)
32F	L	1	4000	80	10	4	Cophosis	No	90%	na	100%	na	na	1	X	28
43M	Bil	25	4000	5	9	2	20 dB	X	70%	0%	0%	na	na	9	No	24
40F	L	2	6000	75	9	4	85 dB	X	70%	20%	100%	30%	100%	7	X	21
53F	L	4	6000	25	9	4	Cophosis	X	80%	40%	100%	na	na	8	X	18
49F	L	1	4000	45	10	4	90 dB	X	50%	40%	na	40%	na	8	X	17
38F	R	10	6000	15	9	3	80 dB	X	70%	30%	100%	na	na	2	X	12
53M	Bil	5	16,000	10	8	2	20 dB	X	65%	0%	na	na	na	8	No	11
40F	L	3	16,000	25	10	4	80 dB	X	60%	10%	na	20%	na	8	No	8
40M	L	5	7000	5	7	3	90 dB	NB	70%	20%	na	na	na	6	X	8
								NB								
62M	R	3	8000	5	8	4	30 dB	X	70%	0%	na	0%	na	8	No	5
51F	L	5	1000	20	9	4	Cophosis	X	85%	50%	na	na	na	4	X	2
46M	R	1	8000	20	9	4	65 dB	NB	75%	na	85%	na	na	2	X	3
								No								

Notes: T: tinnitus; M: male; F: female; L: left; R: right; Bil: bilateral; T duration: tinnitus duration in years; dB: decibel; VAS: visual analogue scale; T grade: tinnitus grade using Tinnitus Questionnaire (Goebel and Hiller, 1994); T noise: tinnitus presents as noise-like sound; NB: narrow band; TMS: transcranial magnetic stimulation; ED supp N: amount of noise-like tinnitus suppression using extradural stimulation; ED supp PT: amount of pure tone tinnitus suppression using extradural stimulation; ID supp N: amount of noise-like tinnitus suppression using intradural stimulation; ID supp PT: amount of pure tone tinnitus suppression using intradural stimulation; na: not applicable; IPG: internal pulse generator implanted.

neuronavigation-guided TMS in patients with pain not responding to medication and dorsal column stimulation (DCS) except for one patient who had refused DCS because of paresthesia. The other patient had trigeminal neuropathy.

Guided by the fMRI, stereotactic TMS of the SSC was performed. Five (one male, four females) of the eight participants experienced a decrease in their pain by more than 50% from this non-invasive test stimulation. Three of these participants had iatrogenic peripheral nerve lesions, resilient to DCS; one had a lesion in the supraorbital nerve that occurred through removal of a cutaneous tumor, the lateral sural cutaneous nerve had been cut during knee surgery in one participant; and another had a medial brachial cutaneous nerve lesion. The five participants who were responsive to TMS subsequently underwent fMRI-based neuronavigated implantation of an epidural electrode on the SSC on the area where the cortical fMRI signal changed as result of allodynia. The results of the treatment was evaluated by means of a visual analogue scale (VAS) at monthly intervals up to 3 months, at 6, 9, and 12 months.

The three participants who had less than 50% pain reduction from TMS suffered from a lesion of the supraorbital nerve, burning feet, and a nerve lesion of the right thumb.

fMRI

fMRI was performed on a 3T MR system using the blood oxygen level dependent (BOLD) method and consisted of acquisition of whole brain FFE-EPI images (resolution of $3 \times 3 \times 4$ mm, TE/TR = 33/3000 ms) as well as high resolution T1 weighted anatomical images. The stimulation paradigm was a blocked fMRI design alternating 30 s epochs of sensory stimulation (tactile allodynia) with 30 s epochs of non-stimulation (rest). Statistical comparison of brain activity during tactile skin stimulation to rest *results* in a significant area of activity in the contralateral post-central gyrus corresponding to the somatotopic area of perception of pain located within the primary and secondary sensory cortex. Other areas of activity are found in ipsilateral primary sensorimotor cortex,

supplementary motor area, and cerebellum, and are related to the motor activity of the hand contralateral to the painful area. BOLD signals were also noted in the contralateral parietal cortex, contralateral inferior frontal cortex, and bilateral insula, confirming the results of an earlier study (Maihofner et al., 2004).

Transcranial magnetic stimulation

TMS was performed with a Super Rapid magnetic stimulator (Magstim Inc., Wales, UK) allowing stimulation in a range of 1–50 Hz. Magnetic stimulation is performed using neuronavigation-guided localization of the area of cortical fMRI signal change induced by allodynia. The duration of a TMS session is ~1 h. As the pain suppressing effect of TMS is varying but shortlasting, only VAS data are used as assessment for pain improvement. Several series of 200 pulses each of TMS at a strength of 90% of the motor threshold (MT) were applied at frequencies of 1, 5, 10, and 20 Hz. If pain suppression was obtained, placebo stimulation at the same site was performed by holding the coil perpendicular to the skull. Stimulation at 110% MT was also tested to exclude that pain reduction was actually caused by motor cortex stimulation. In the patients who had more than 50% pain reduced from TMS an epidural electrode was implanted over the area of cortical signal change as located by fMRI-based neuronavigation. This is the same protocol as described for tinnitus suppression (De Ridder et al., 2005, 2006).

Medication

All participants used or had used tricyclic antidepressant drugs, anti-epileptics such as gabapentine and clonazepam, and painkillers such as tramadol or fentanyl patches. Medication was unaltered before TMS up to the moment after complete implantation of the epidural electrode. Following surgical implantation of the electrode the patients were advised to decrease their medication intake by decreasing the daily dose of their medication by half every subsequent week.

Surgical procedure

After making a small craniotomy, an octopolar electrode (Lamitrode 44, ANS Inc. Plano, TX, USA) is positioned epidurally and sutured to the dura to obtain firm contact and avoid displacement of the electrode. The stimulating electrode was placed over the area of BOLD activation using fMRI-based frameless stereotactic guidance (Treon, Sofamor Danek, CO, USA). The electrode was connected to an extension wire that was passed outside the skin and connected to an external pulse generator. After 1 month of bipolar trial stimulation the participant is evaluated (VAS) and if considered successful the electrode is connected to an internal pulse generator (IPG) implanted in a subcutaneous pouch (Genesis XP). The postoperative course was uneventful in all five participants. No epileptic seizures were elicited by the stimulus parameters used, and no anti-epileptic drugs were administered prophylactically.

Electrical stimulation parameters

External trial stimulation

In contrast to DCS no paresthesia are evoked, except at high intensity stimulation. High intensity, high frequency stimulation induced worsening of the pain in three of the participants. Using stimulation parameters that suppressed pain the participants felt no side effects, and were unable to detect whether the stimulation was on or off. This allowed for selecting stimulation parameters in a placebo-controlled way.

All eight poles of the paddle lead were individually and separately turned negative with the other seven electrodes positive. The best electrode setting was subsequently refined by turning positive electrodes negative or neutral up to the moment the participant experienced the best pain suppression.

The stimulation parameters were adjusted individually to obtain the best pain suppression and the least side effects. The frequency adjusted first from 2 to 40 Hz in steps (2, 4, 6, 10, 20, and 40 Hz) and subsequently the stimulus current was increased or decreased depending on whether the

stimulation decreased or increased the pain, from 0.2 to 10 mA (0.2–3 mA in increasing steps of 0.2 mA to be followed by steps of 0.5 mA up to the moment of worsening pain). Once pain relief is obtained pulse width was set at the shortest duration (between 52 and 390 μ s).

All TMS and electrical stimulations were approved by the ethical committee of the University Hospital Antwerp, Belgium.

Results

Tinnitus

Results from electrical stimulation via extradural implanted electrodes demonstrated a highly significant tinnitus suppression for pure tone tinnitus ($U = 25$, $p < 0.01$) in comparison to noise-like tinnitus, with an average pure tone tinnitus suppression of 97% versus 24% for noise-like tinnitus (De Ridder et al., 2006) (Table 1).

Neuropathic pain

Transcranial magnetic stimulation

TMS was applied at 90% of the MT to the target area of the SSC using neuronavigation. That stimulation caused a reduction of at least 50% of the pain in five of eight patients. One of the other three patients experienced no relief and the other two had some relief ($< 50\%$). One of these patients had similar pain relief from placebo stimulation. Those three patients were excluded from further studies. TMS at 110% MT on target did not elicit any motor activity in any of the five participants.

Typically the participants did not feel paresthesia during the TMS stimulation. The duration of the effect of the TMS differs individually, lasting from 5 s up to 2 min (median 60 s for 5 Hz stimulation).

Electrical stimulation

Internal IPG stimulation: All participants are stimulated at low frequencies (4–8 Hz), with mid range

Table 2. Stimulation settings for the somatosensory cortex electrodes

Patient number	Frequency (Hz)	Pulse width (μ s)	Electrodes	Min. Amp. (mA)	Max. Tol. Amp. (mA)	Cycle on (h/m/s)	Cycle off (h/m/s)
1	8	390	0000+--+	0.5	3.0	00/01/00	00/01/00
2	4	52	00000--+0	0.1	3.0	00/01/00	00/00/30
3	6	299	0+-+0+-+	2.0	7.0	00/00/10	00/00/10
4	6	299	0++00--0	0.5	4.0	00/01/00	00/01/00
5	4	390	0++0+-+--	4.0	7.0	00/01/00	00/00/30

Note: Min. Amp, minimal amplitude, lowest stimulation amplitude setting; Max. Tol. Amp, maximally tolerable amplitude; h/m/s, hours/minutes/seconds.

Table 3. Results from the five patients who underwent an implantation of an epidural electrode on the SSC after successful TMS

Patient number	Gender	Age	Cause	Pain duration (years)	Follow-up (months)	VAS pre-implant	VAS post-TMS	VAS 3 month post-implant	VAS at last follow-up visit	Percentage VAS decrease; baseline: last visit
1	F	42	Stroke	10	6	10	0	1	1	90
2	F	55	Nerve lesion	10	23	10	0	0	0	100
3	F	43	Syringomyelia	1	13	9	0	0	0	100
4	M	46	Nerve lesion	15	8	8	4	3	2	75 ^a
5	F	49	Nerve lesion	4	13	9	1	3	3	66

^aAfter repositioning of the electrode the patient improved.

pulse widths (299–390 μ s) except for one participant (52 μ s), and with variable amplitudes. Stimulation parameters were set in an on/off cycling mode, with stimulation on for 10–60 s and off for 10–30 s (Table 2).

The participants who underwent the electrode implantation obtained a pain decrease varying between 66% and 100% (median 90%) at the last follow-up visit. One of the participants (no. 4) improved after repositioning the electrode. The clinical benefit of the electrical stimulation parallels the short-lasting improvement with TMS (Table 3).

Based upon the VAS's psychometric properties such as standard error of measurement and confidence interval (Jensen et al., 1999), significant pain suppression was found in all of the five pain participants after primary SSC stimulation. A significant pre versus post difference on a 95% probability level should be equal to or above 1.87, on a 99% probability level equal to or above 2.46, whilst the highly significant average pain reduction was equal to 8.

Average follow up was 12 months (range between 6 and 23 months) (Table 3).

Postoperative computerized tomography (CT) scans were performed and merged with the pre-operative fMRI and proved a correct position of the paddle lead on the area of fMRI signal change on the SSC (Fig. 1).

Medication

After implantation the medication used is individually tailored to the beneficial effect of the neuromodulative treatment (Table 4).

Case report

This is an example of treatment of a patient who presented with unilateral right frontal neuropathic pain.

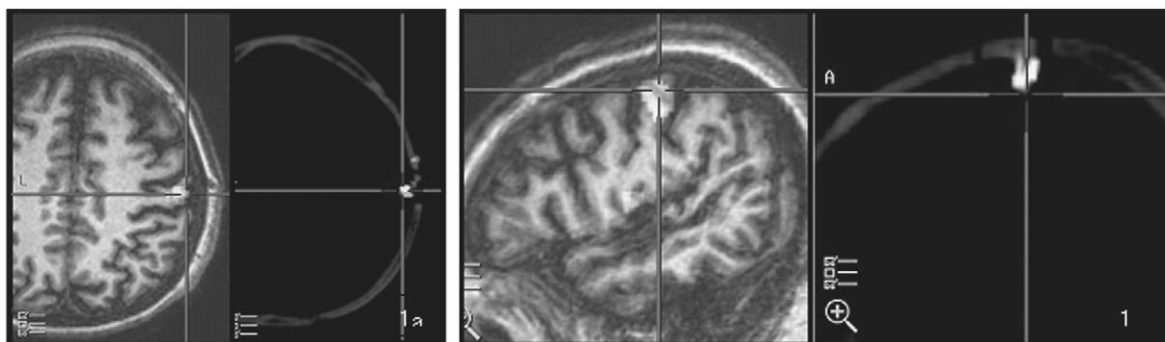


Fig. 1. Crosshairs mark the targeted area on preoperative fMRI and the correlating postoperative location of the paddle lead (CT) on axial (1a) and sagittal view (1b).

History

A 53-year-old woman presents with a 10-year history of persistent lancinating pain in the right supraorbital region. The pain arose a few weeks after a surgical excision of basal cell carcinoma on the right side of the forehead. Initially she suffered a normal postoperative pain progressively evolving to a constant, sharp lancinating pain. Multiple surgical procedures that followed caused aggravation of the symptoms.

Except for the pain she also developed a sensation of her right eye being located on her right maxillary arc. Despite a normal vision as demonstrated by an extensive neuro-ophthalmological work-up, the phantom sensation often induced a misperception of the position of surrounding objects causing her to run into obstacles ipsilateral to the phantom sensation.

Clinical examination

The presence of hyperalgesia (exaggerated reaction to painful stimuli) and a loss of sensation of temperature and vibration in the right V1 dermatoma were noted. Tactile stimulation of the medial cornea and upper eyelashes of the right eye were sensed at the phantom eye at the right maxillary arc (Fig. 2). Tactile stimulation of the medial cornea and medial upper and lower eyelashes of the phantom eye were referred to the corresponding areas at the ipsilateral eye. Phantom corneal reflex

could not be elicited. Further clinical exams were normal.

fMRI

fMRI was performed on a 3T MR system using the BOLD method and consisted of acquisition of whole brain FFE-EPI images (resolution of $3 \times 3 \times 4$ mm, TE/TR = 33/3000 ms) as well as high resolution T1 weighted anatomical images. The stimulation paradigm was a blocked fMRI design alternating 30 s epochs of sensory stimulation (the patient rubbed the painful right V1 skin area using her left hand) with 30 s epochs of non-stimulation (rest). Statistical comparison of brain activity during skin stimulation to rest resulted in a significant area of activity in the left post-central gyrus corresponding to the area of perception of pain located within the left primary sensory cortex (Fig. 3). Other areas of activity were found in left primary sensorimotor cortex, supplementary motor area, and left cerebellum, and are related to the motor activity of the left hand and arm rubbing the right V1 skin area.

Transcranial magnetic stimulation

TMS was performed with a Super Rapid magnetic stimulator (Magstim Inc., Wales, UK) allowing stimulation in a range of 1–50 Hz. Magnetic stimulation is performed after neuronavigation-guided localization (Stealth, Sofamor Danek, CO, USA)

Table 4. Modification of medication before electrode implantation and at last follow-up visit

Patient number	Baseline medication before electrode implantation					Medication at last follow-up visit				
	Gabapentine daily dose (mg)	Clonazepam daily dose (mg)	Amytriptiline daily dose (mg)	Tramadol daily dose (mg)	Fentanyl patches	Gabapentine daily dose (mg)	Clonazepam daily dose (mg)	Amytriptiline daily dose (mg)	Tramadol daily dose (mg)	Fentanyl patches
1	2400	S	S	600	200	0	–	–	0	25
2	900	2	S	200	S	0	2	–	0	–
3	1200	2	S	200	S	300	2	–	0	–
4	1800	S	S	400	S	0	–	–	100	–
5	S	S	S	400	S	–	–	–	0	–

Note: S: Previously used drug but stopped because of lack of effect or side-effects.



Fig. 2. Drawing of phantom eye. The phantom eye is located on V2, inferior and lateral to the real eye, slightly tilted. Only the medial eyelashes are felt ectopically (picture with permission of the patient).

of the area of cortical reorganization based on the predefined area on the fMRI. Several series of stimulation are applied with different frequencies and intensities on target and adjacent areas.

The TMS caused a maximum reduction of 80% of the supraorbital pain and a complete disappearance of the phantom sensation.

The suppression of the pain was obtained immediately after starting the TMS and had a residual effect whereas the phantom shifted back to its normal position after a longer period of stimulation.

TMS on target (Fig. 2) using a rate of 1 pulse per second (pps) during 60 s at an intensity of 90% MT caused an immediate pain reduction of 80% and complete disappearance of the phantom sensation after 25 s of stimulation. The same pain relief was obtained with TMS at a rate of 5 pps and 90% MT but the phantom eye shifted back in 10 s. TMS with 10 consecutive 500 ms bursts at 20 pps at 90% MT had no beneficial effect on the pain or the phantom. Lowering the output to 80% MT at a rate of 1 pps still induced an 80% pain reduction

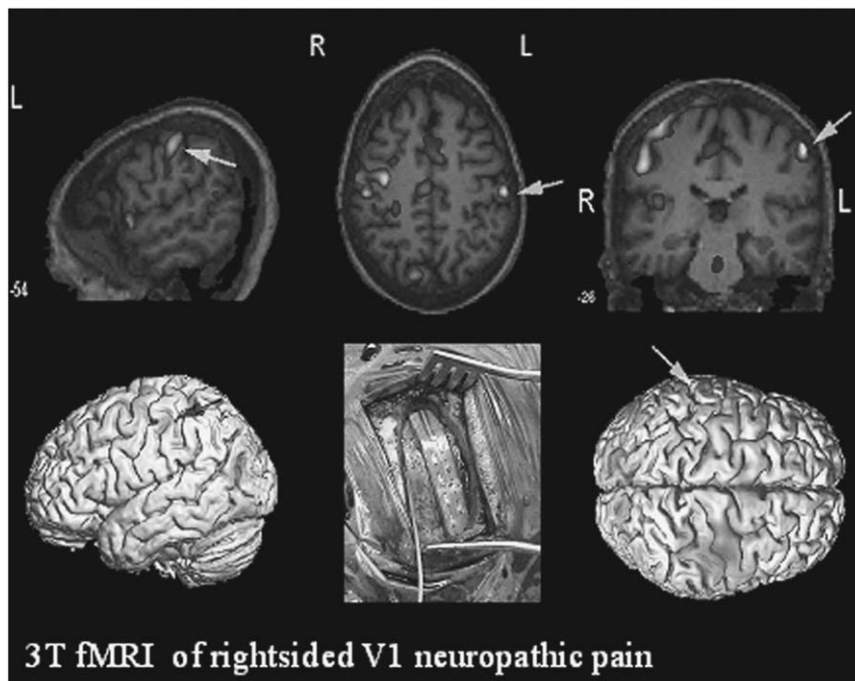


Fig. 3. fMRI activity overlaid on sagittal, transverse, and coronal slices as well as a surface reconstruction of the patient's brain. Arrow indicates area of V1 pain sensation, located within the left post-central gyrus. Other areas of activity were found in left primary sensorimotor cortex, supplementary motor area, and left cerebellum and are related to the motor activity of the left hand and arm rubbing the right V1 skin area. Inset: View of extradural electrode positioned overlying area of BOLD activation.

but the phantom progressively disappeared after 35 s of stimulation. Sham stimulation had no effect. TMS at 110% MT did not elicit any motor activity.

Consecutively an epidural octopolar electrode (Lamitrode 44, ANS Inc., TX, USA) was implanted for electrical stimulation of the area of BOLD activation on the primary SSC elicited by worsening the pain using tactile stimulation (allodynia). The electrode was located at the predefined target using fMRI-based frameless stereotactic guidance. The leads of the electrodes were tunneled subcutaneously to the abdominal wall and connected to the IPG (Genesis, ANS Inc., TX, USA) and implanted in a subcutaneous pocket. The postoperative course was uneventful.

After recovery from the surgery the patient felt the same pain and phantom sensation as preoperatively. On the first postoperative day the IPG was activated and a complete suppression of pain and a complete disappearance of the phantom eye was obtained. Stimulation parameters were set in an alternating 30 s ON and 60 s OFF mode with 52 μ s pulse width, 4 pps at 1.0 mA. Stimulating with these parameters induced paresthesia in the right supraorbital region. Lowering the intensity to

0.3 mA had a similar effect on the pain and phantom but without any paresthesia. Furthermore the patient had no problem in determining the exact position of surrounding objects after stimulation parameters were set.

Patient was discharged 4 days after surgery completely free of pain and phantom sensation and remained as such after 24 months follow-up.

Postoperative images revealed a correct position of the lead on the primary SSC and not on the motor cortex (Fig. 4).

Discussion

The analogous pathophysiologic mechanisms, symptoms, and imaging results suggest that phantom sounds and phantom pain might be treated using a similar approach. We therefore used a method, previously described for phantom sound suppression, and translated this surgical philosophy to the somatosensory system.

Magnetoencephalographic data integrated with magnetic resonance imaging (MRI), also known as magnetic source imaging (MSI) have demonstrated that neuropathic pain is correlated with a reorganization of the SSC and the intensity of the associated pain is directly correlated to the amount of cortical reorganization (Flor et al., 1995).

Most cortical pain modulating treatments have targeted the motor cortex (Tsubokawa et al., 1991a; Meyerson et al., 1993; Nguyen et al., 1997, 1999). This approach has been based on Penfield's observation that electrical stimulation of the motor cortex in a patient who previously underwent surgical resection of the corresponding SSC as a treatment for epilepsy could produce sensory responses (Penfield and Jasper, 1954; Lende et al., 1971).

Other studies have shown that hyperactive thalamic neurons can be inhibited by motor cortex stimulation in patients with deafferentation pain whereas stimulation of the SSC had no effect on the thalamic firing rate (Rinaldi et al., 1991; Tsubokawa et al., 1991a, b; Lenz et al., 1998). In humans selective TMS to the primary SSC is sufficient to abolish perception of cutaneous stimulation of the corresponding skin area (Hannula



Fig. 4. Postoperative X-ray demonstrating the position of the lead.

et al., 2005) and to induce a disruption of tactile discrimination (Knecht et al., 2003), however its mechanism is unknown. But it has been shown in mice that SSC stimulation can activate inhibitory networks in the thalamic reticular nucleus (Zhang and Jones, 2004). Whether the clinical beneficial effect of SSCs is dependent on activation of inhibitory feedback mechanisms via the thalamic reticular nucleus still has to be demonstrated in humans. Whether or not SSC stimulation is capable of treating the same patients as motor cortex stimulation or a different subset of patients suffering from sensory deprivation induced pain is to be investigated.

Conclusion

The results of this study suggest that electrical stimulation of the auditory cortex and SSC might be a valid option for tinnitus and pain control in a selected subset of patients. The patients of the present study were selected on the basis of test stimulation using fMRI-based and neuro-navigation-guided TMS as a non-invasive preoperative tool.

The results also strengthen the hypothesis that the pathophysiology of some forms of tinnitus is similar to that of some forms of neuropathic pain.

Abbreviations

BOLD	blood oxygen level dependent
CT	computerized tomography
DSC	dorsal column stimulation
fMRI	functional MRI
GABA	gamma amino butyric acid
IPG	internal pulse generator
MRI	magnetic resonance imaging
MSI	magnetic source imaging
MT	motor threshold
NMDA	N-methyl-D-aspartic acid
PET	positron emission tomography
SSC	somatosensory cortex
TMS	transcranial magnetic stimulation
VAS	visual analogue scale

Acknowledgments

The authors thank Dr. Edwin Verstraeten for his help in the statistical analysis of the data, and ANS Medical and Tim Vancamp for the support of this study.

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CHAPTER 37

Trans-electrical nerve stimulation (TENS) for somatic tinnitus

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Abstract: The somatic tinnitus syndrome includes those forms of tinnitus that are associated with a somatic disorder involving the head and upper neck. It has been suggested that physiological mechanisms where interactions occur between the somatosensory and auditory systems are the etiology for that kind of tinnitus. Trans-electrical nerve stimulation (TENS) of areas of skin close to the ear increases the activation of the dorsal cochlear nucleus through the somatosensory pathway and may augment the inhibitory role of this nucleus on the CNS and thereby ameliorate tinnitus. In a prospective descriptive study of 26 patients with the probable diagnosis of somatic tinnitus we found that TENS could improve the tinnitus in 46% of the participants (23% did not hear it anymore, and in 23% its intensity was reduced). VAS scores improved from 6.5 to 6.0 after 2 weeks of treatment ($p < 0.01$). Patients used TENS at home for 2 h, once per day during 2 weeks (alternating ramped burst, 150 pps, with pulse duration of 100 μ s, amplitude 0–60 mA; average TENS intensity was 27 mA). Intermittent “typewriter” type of tinnitus was the most responsive. Somatic tinnitus without otologic disease had better response than tinnitus associated to otological causes ($p = 0.047$).

Keywords: tinnitus; somatic tinnitus; transcutaneous electric stimulation; myoclonus; temporomandibular joint

Introduction

Levine (1999, no. 1450) has defined the “somatic tinnitus syndrome” as unilateral tinnitus temporally associated and ipsilateral to a somatic disorder involving the head and upper neck (see Chapter 17). It has been suggested that a physiological mechanism where interactions between the somatosensory and auditory systems occur is the cause of some forms of tinnitus or the modifying factors of tinnitus.

Neck and orofacial movements can often modulate the tinnitus as can movements of upper extremities, tactile stimulation (Cacace et al., 1999, no. 622), changes in gaze (Cacace et al., 1994, no. 620), temporomandibular joint (TMJ) disorders (Morgan, 1992, no. 1500), teeth manipulations, etc. Möller et al. (1992) demonstrated that 40% of individuals with tinnitus changed their tinnitus with median nerve stimulation. According to Rubinstein (1993), 30% influenced their tinnitus with TMJ movements). Sánchez et al. (2002) showed that 65% could change their tinnitus with any orofacial muscle contraction and Levine et al. (2003) increased it up to 80% of the participants in

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Shulman's study is the comparison with a control group presented by Thedinger. Dobie et al. (1986) in a double blind clinical trial reported similar poor results.

Electrical stimulation of the skin near the ear is not likely to have its effect on the cochlea but it is rather a form of somatosensory stimulation that has its effect on the auditory nervous system. Other kinds of electrical stimulation directly applied to the cochlea are assumed to affect the receptors in the cochlea. Animal experiments have shown that passing electrical current through the cochlea can affect discharges in auditory nerve fibers (Konishi et al., 1970, no. 1389). Using this approach to tinnitus, Cazals et al. (1978) reported that 80% of 15 profound deaf patients experienced suppression of their tinnitus after the application of DC on the promontory or the round window. The stimulation applied to the round window gave better results. No patient showed residual inhibition.

One of the largest studies is the one carried out by Steenerson and Cronin (2003). Five hundred tinnitus patients were treated with probe electrical stimulation. Causes were very heterogeneous (sensorineural hearing loss, Ménière's disease, head and acoustic trauma, etc.). The results showed 53% of tinnitus improvement (subjective rating scale). After 3 months, 72% of them maintained the benefits of the treatment.

Rubinstein et al. (2003) studied the effect of electrical stimulation of the cochlea with high rate pulse trains (500 pps) applied to the round window in 11 patients with high frequency hearing loss and tinnitus. Substantial or complete tinnitus suppression with a residual inhibition from 45 min to 72 h was present in 45% of the patients.

Our objective was the description of the effect of TENS in the treatment of somatic tinnitus.

Materials and methods

Twenty-six patients, 13 men and 13 women were entered into a prospective descriptive study. The patients were referred to our tinnitus clinic from January 2005 to January 2006. Age average was 49 ± 14 years old. The left ear was more commonly

affected than the right one (38.5% vs. 11.5%). Tinnitus was bilateral in 38.5% of the patients and cephalic in two cases (7.7%). Time from symptom debut to first visit in our clinic was 19 ± 29 months.

Hearing impairment (≥ 25 dB in at least one frequency) was present in 50%. Hearing loss was principally in the right ear (61.5%); the left ear was affected in 30.8% and it was bilateral in one case (7.7%).

Somatic tinnitus for more than 6 months was diagnosed according to two criteria: first, an acute somatosensory event as the trigger for tinnitus appearance; second, tinnitus with evident modulation with orofacial movements or posture changes. Eight patients (30.8%) had intermittent "typewriter tinnitus", highly modified by jaw movements. Four of the participants had tinnitus secondary to a cervical spasm or whiplash syndrome (15.4%). Two participants had a TMJ event just previous to their tinnitus and in other two, the tinnitus was possibly triggered by extraction of a molar. Eight participants had otological causes for the tinnitus (chronic otitis media, sensorineural hearing loss) but orofacial movements could modulate their tinnitus. In two participants the cause of the tinnitus was uncertain.

Only patients who were able to change their tinnitus intensity or frequency by orofacial, cervical, or TMJ movements (tinnitus somatic test, Levine, 2004) were included. Five patients had TMJ problems and could change their tinnitus by moving their jaw, three patients had cervical problems and could change their tinnitus by turning their head. In four patients, tinnitus changed with certain orofacial movements.

Initial tinnitus evaluation consisted in a questionnaire (*Cuestionario Inicial de Acúfenos, CIA*), filled by the patient before inclusion in the study. CIA included visual analog scales (VAS) to assess the intensity and annoyance for the tinnitus, hearing impairment, hyperacusis, and a validation into Spanish of the tinnitus handicap inventory — THI (Herraiz et al., 2001). Psychoacoustic evaluation (tinnitogram), including pitch, loudness, minimal masking level, and residual inhibition matching (effect on tinnitus intensity after 1 min masking sound exposure) was done.

The TENS employed is the model Epix XL (Empi, Minnesota). The method used for electrical stimulation was demonstrated and explained to the patients in the office and after that, the patients had to use it at home for 2 h, once per day during 2 weeks. The program for stimulation consisted of alternating ramped bursts, 150 pps, with pulse duration of 100 ms. The patients could vary the intensity of the current between 0 and 60 mA. The negative electrode was always placed on the skin of the mastoid. In patients whose tinnitus could be modified by jaw movements, the positive electrode was placed on the skin of the TMJ. Patients with cervical problems placed the positive electrode on the sternocleidomastoid muscle. If tinnitus was bilateral, we used two stimulation channels: each negative electrode was placed on the mastoid bone whereas the positive one was placed on the TMJ or the sternocleidomastoid muscle according to the etiology or the tinnitus modifying maneuver. The patient adjusted the intensity to the highest possible, keeping a comfortable sensation.

Patients were evaluated after 2 weeks of treatment at which time the patients were asked: “do you feel better, same or worse after the treatment?” A VAS on tinnitus intensity was used to evaluate the intensity of the tinnitus. Statistical analysis of the results was performed using SPSS 13.0 software program. Significance was considered when $p < 0.05$.

Results

Tinnitus pitch is described in Table 1. Loudness average was $14\text{ dB} \pm 9$ and the minimum masking level was $12\text{ dB} \pm 8$. VAS average before treatment was 6.5 ± 1.9 and the THI average score was

$41\% \pm 24$. Fifty percent of the participants could always perceive their tinnitus and 70% referred intensity changes along the day. Intense external sound reduced tinnitus perception in 64% of the patients. Positioning changes or orofacial movements could increase tinnitus perception in 73%.

After TENS treatment, 46% of the patients reported improvement in their tinnitus: 23% did not hear it anymore (6 patients), and 23% had reduced intensity (6 patients). Tinnitus increased temporally in one participant but returned to the initial level later (Fig. 2). VAS was reduced significantly after treatment (from 6.47 to 6.0, $p < 0.01$). The average TENS intensity used was 27 mA. Three patients decided to continue the treatment for another 2 weeks and a fourth one continued for 4 weeks. Two patients referred enough improvement to stop TENS after the first 2 weeks. Tinnitus disappeared in rest of the six participants.

A better result was obtained in non-persistent tinnitus (nine patients improved, $p < 0.05$) compared to continuous tinnitus (three patients improved). Other characteristics as shorter time of evolution or higher initial THI and VAS scores showed a better response but there were not statistical differences.

We divided the sample in two groups according to otologic etiology or somatosensory event-related etiology. Somatic tinnitus not associated to any otological disease improved in 59% of the

Table 1. Tinnitus pitch

	8 kHz	6 kHz	4 kHz	2 kHz	1 kHz	0.5 kHz
PT	5	1	2	–	4	2
NBN	2	1	5	1	–	–

Note: PT, pure tone; NBN, narrow band noise.

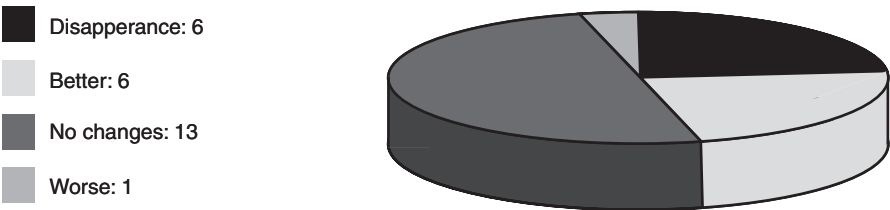


Fig. 2. Response to TENS treatment after 2 weeks. Tinnitus improvement was referred by 46% of the patients (disappearance + better). (See Color Plate 37.2 in color plate section.)

patients, while those somatic tinnitus related to otologic diseases only improved in 14% of the participants ($p = 0.047$). The group of intermittent “typewriter” tinnitus was the most responsive: 88% improved or eliminated their tinnitus.

We did not find any differences in the results of TENS on age, gender, side of the tinnitus, tinnitus pitch or modifying factors (external sound, anxiety, positional changes, and orofacial movements).

Discussion

Our results confirm that TENS can be an option for somatic tinnitus management. As we have described in the introduction, the benefit of electricity for tinnitus has been tested and results have been presented in many studies. The main difference of our protocol with the rest published ones is the exclusive inclusion of somatic tinnitus patients in our study. The “somatic tinnitus syndrome” is a quite new concept in tinnitus science and it has to be defined in its characteristics and limits. Many forms of somatic tinnitus can have a multi-etiological origin and other diagnosis can be difficult to exclude. There are not specific measurement processes to confirm this entity so the clinical report is the key for diagnosis. We find very interesting the use of the somatic tinnitus test proposed by Levine (2004), as a helping tool for somatic tinnitus diagnosis.

Comparison with other studies is hardly difficult due to the variability of etiologies included, the TENS protocol used, and the different outcome measurement among the authors. In a study by Steenerson and Cronin (2003), 53% of the patients improved according to VAS evaluation using electrical stimulation of the skin near the ear. Other authors like Rubinstein et al. (2003) showed improvement in 45% through electrical stimulation of the round window. Our protocol achieves 46% of the patients decreased their somatic tinnitus and 88% of typewriter tinnitus patients showed a complete elimination or a reduction in their perception. There are many programs to be used, places to set the electrodes, type of electrical current, duration of the stimulation, etc. and all these possibilities should be standardized. The efficacy of

TENS in somatic tinnitus does not rule out the treatment of non-somatic tinnitus with the same system, if it could demonstrate an influence of the somatosensory neural path over the central auditory in other tinnitus etiologies.

Conclusions

TENS improves 46% of our somatic tinnitus patients, and reduces statistically VAS scores after 2 weeks of treatment. Intermittent typewriter tinnitus was the most responsiveness diagnosis. Tinnitus caused by a somatosensory injury had better response than somatic tinnitus with an otologic disease. Standardizing the indications and method could increase the efficacy of electrical stimulation in somatic tinnitus.

Abbreviations

AC	alternating current
CIA	Cuestionario Inicial de Acúfenos
CNS	central nervous system
DC	direct current
DCN	dorsal cochlear nucleus
TENS	trans-electric nerve stimulation
THI	tinnitus handicap inventory
TMJ	temporomandibular joint
VAS	visual analog scale

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Plate 34.2. Laboratory setting: rTMS application in a tinnitus patient. The neuronavigational system (1) is used to determine the optimal position of the stimulation coil (2) in relation to the patient's skull. (For B/W version, see page 364 in the volume.)

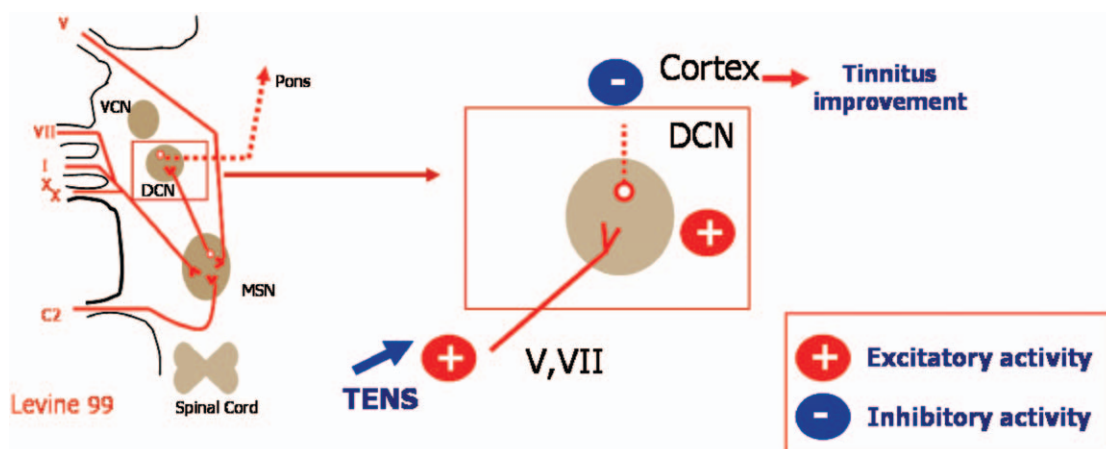


Plate 37.1. Representation of the pathways involved in somatic tinnitus modulation. We show the possible place where the trans-electrical nerve stimulation could act and reduce tinnitus intensity. The effect of TENS in the somatic tinnitus could restore the dorsal cochlear nucleus (DCN) inhibition through the electrical stimulation of the somatic pathway. (For B/W version, see page 390 in the volume.)

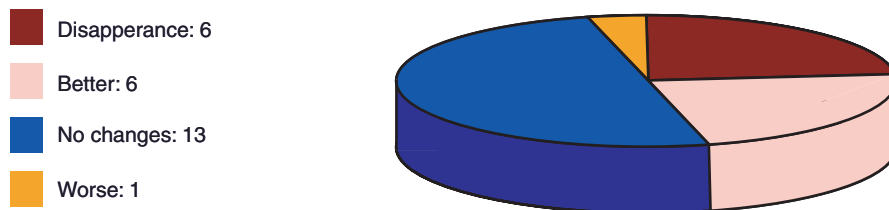


Plate 37.2. Response to TENS treatment after 2 weeks. Tinnitus improvement was referred by 46% of the patients (disappearance + better). (For B/W version, see page 392 in the volume.)

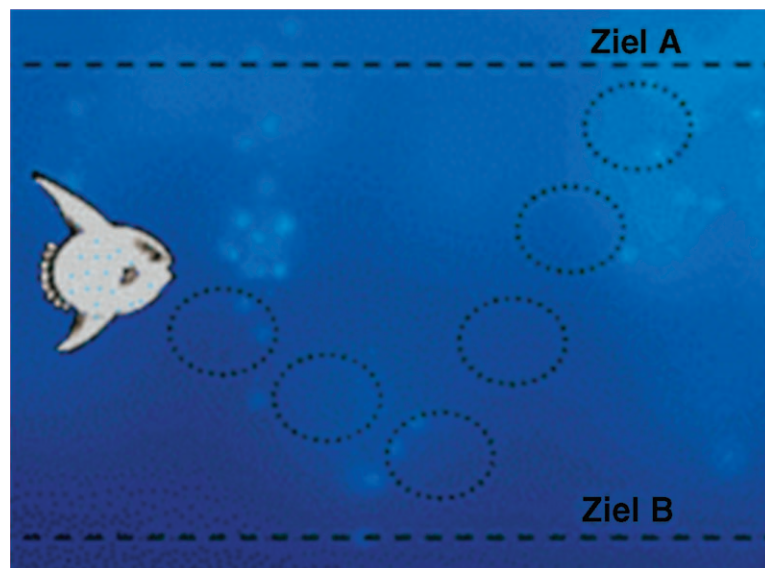


Plate 46.2. The schematic fish on the patient monitor that was to be “moved” up or down (depending on the feedback protocol) during neurofeedback training. The height of the fish represented the amplitude/power of the specific frequency band. (By courtesy of Eldith© Corporation, Germany.) (For B/W version, see page 477 in the volume.)

CHAPTER 38

Microvascular decompression operations

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Abstract: Moving a blood vessel off the intracranial portion of the auditory nerve can successfully cure some individuals with specific forms of subjective tinnitus. This operation, known as microvascular decompression (MVD) is in general use to treat other hyperactive disorders such as hemifacial spasm (HFS) and trigeminal neuralgia (TGN) where the operation has a success rate of approximately 85%. MVD for tinnitus has lower success rate. MVD operations have also been used to treat some forms of vestibular disorders, disabling positional vertigo (DPV). In a study of treatment of a selected group of 72 patients with severe tinnitus and signs of change in the conduction properties of the auditory nerve 13 (18.2%) had total relief from tinnitus after MVD, 16 (22.2%) had marked improvement, 8 slight improvement and 33 (45.8%) no improvement. Two patients became worse (2.8%). There were 40 men and 32 women in the study group and there was considerable difference in the success rate for men and women. Fifty-five percent of the women and 29% of men showed relief or improvement. The success of the operation depended on the length of time the participants in the study had had their tinnitus and it was best for those who had had tinnitus for less than 3 years. The success rate for bilateral tinnitus was much lower than for unilateral tinnitus.

Keywords: tinnitus; microvascular decompression; auditory nerve

Introduction

Vascular compression of the root of cranial nerves, or rather close contact between a vessel and a cranial nerve, is associated with hyperactive disorders of which trigeminal neuralgia (TGN) and hemifacial spasm (HFS) are the best known (Møller, 1993). Microvascular decompression (MVD) of cranial nerves is a common treatment for these disorders, and the success rate of MVD for TGN is approximately 85% (Barker et al., 1996) and it is similar for HFS (Barker et al., 1995) or higher (Møller and Jannetta, 1987). MVD operations for

these two disorders have been performed routinely at least for the past 25 years (Møller, 1998).

A vestibular disorder known as disabling positional vertigo (DPV) can be cured by MVD of the intracranial portion of the vestibular nerve (Jannetta and Sekhar, 1986; Møller et al., 1986). When patients for such operations are selected according to specific criteria (Møller et al., 1993b) the success rate of the MVD operation (free of symptoms or markedly improved) was reported to be 79% in a study of 207 patients (Møller et al., 1993b) thus slightly less than the success rate for TGN and HFS. While MVD is the only known treatment for HFS that provides total relief of symptoms, other treatments are available for TGN and DPV.

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Only a few studies of the results of MVD operations for tinnitus have been published involving much fewer patients than studies of MVD operations for TGN and HFS. The reported results of MVD operations for tinnitus are not nearly as encouraging as they are for TGN, HFS or DPV. While diagnosis of TGN and HFS can be done from the patient's history, patient selection for the MVD operation to treat DPV is more complex and it is even more complex and demanding to select tinnitus patients for MVD operations. None of the disorders that can be cured by MVD operations is life threatening and the decision about operation depends on the patients' decision regarding benefits and risks. MVD operations require special skill of the surgeon and surgeons who do many such operations obtain the best results and the fewest side effects. In the hands of experienced surgeons, risks in connection with the operation are small but some complications are potentially catastrophic.

The pathophysiology of cranial nerve vascular compression disorders is poorly known (Møller, 1993). Two hypotheses have prevailed, one assuming a local effect on the nerve causing ephaptic transmission between denuded nerve fibers (Gardner, 1966); the other hypothesis assumes that the symptoms are caused by physiologic abnormalities in central nervous system structures (nuclei) (Møller, 1993, 1999). Physiological evidence from electrophysiological recordings during MVD operations of patients with HFS indicates that the effect of the close contact between a nerve root and a blood vessel is an irritation of the nerve rather than morphological changes such as demyelination. The results were interpreted to support the hypothesis that abnormal activity created by the irritation from a blood vessel in turn changes the function of more central structures through processes known as "the kindling phenomenon" (Goddard, 1964; Møller and Jannetta, 1984; Møller, 1993), thus a form of expression of neural plasticity (Møller, 2006).

While HFS is treatable by moving a blood vessel off the root of the facial nerve, there is considerable evidence that the anatomical location of the physiological abnormality that causes the symptoms (involuntary muscle contractions and

synkinesis) is the facial motonucleus. Studies on HFS have thus supported the nucleus hypothesis and the results suggest that vascular compression is only one of two or more factors that are necessary for the manifestation of symptoms (Møller, 1993). Similar pathophysiology may be assumed for the other disorders that can be cured by MVD thus indicating a complex pathology involving structures of the central nervous system, where expression of neural plasticity play an important role.

MVD for tinnitus

Microvascular decompression of the auditory nerve intracranially for tinnitus has been described by many investigators (Jannetta, 1975; Kondo et al., 1980; Schwaber, 1992; Møller et al., 1993a; Roland et al., 1995; Brookes, 1996; Ko and Park, 1997; Vasama et al., 1998; De Ridder et al., 2004; De Ridder et al., 2005).

In the largest published study, comprising 72 patients who underwent MVD operations with the indication of tinnitus (Møller et al., 1993a), 13 (18.2%) experienced total relief from tinnitus, 16 (22.2%) showed marked improvement, 8 (11.1%) had slight improvement and 2 patients (2.8%) became worse. There were marked differences in the success rate for men and women and with regard to the time the patients had had their tinnitus. The participants in the study were 40 men and 32 women; 54.8% of the women and 29.3% of men showed relief or improvement of their tinnitus, thus a considerable gender dependence. The success of the MVD operation also depended on the length of time the participants in the study had had their tinnitus. Those who experienced total relief or marked improvement had had their tinnitus for an average of 2.9 and 2.7 years, while those who experienced only slight improvement or did not experience any improvement had had their tinnitus for an average of 5.2 and 7.9 years respectively. (As a reminder of the seriousness of tinnitus it is worth noting that two of those who did not benefit from the MVD operation committed suicide within a year after the operation.) In a later study of a subset of 22 patients from the

above-mentioned study it was found that patients with unilateral tinnitus had much higher rate of relief (64%) of their tinnitus from MVD than patients who had bilateral tinnitus (18%) (Vasama et al., 1998). These patients were operated upon consecutively.

In a study of 59 patients with tinnitus (Ko and Park, 1997), 30 were reported to be free of tinnitus after MVD operations, 21 were much improved, 4 had some improvement, and 4 had minimal improvements or no change.

Since tinnitus that has similar character can have different causes, it is challenging to determine if a patient's tinnitus is related to vascular compression of the root of the auditory nerve. In fact there is considerable evidence that only a small number of individuals with severe tinnitus have vascular compression as a cause of their tinnitus, or probably more correctly stated, only a few individuals with tinnitus can benefit from a MVD operation.

The selection criteria for MVD operations for tinnitus have varied. All the patients for the above discussed study (Møller et al., 1993a) had severe tinnitus and were selected for the operation on the basis of history and to some extent on audiological test results including pure tone audiometry (half octave), speech discrimination test using recorded material (NW6) and recordings of the acoustic middle ear reflex response amplitude in three 5 dB increments using tones at 500, 1000 and 2000 Hz. Narrow dips in the pure tone audiogram, poorer speech discrimination than normal based on hearing loss are signs of involvement of the auditory nerve. Abnormalities in the ABR, in the form of prolonged interpeak latencies I–III and delayed or absent peak II were strong indications of vascular contact with the auditory nerve.

Brookes (1996) in a study of MVD in nine patients with tinnitus initially used air computed tomography (CT) cisternography for diagnosis, and later, fast spin-echo magnetic resonance imaging (MRI) found signs of cochlear nerve vascular compression in nine patients with severe tinnitus. These nine patients subsequently underwent vascular decompression surgery. Tinnitus was completely abolished in three (33%), very significantly improved to a sensation level of

< or = 10 dB in four (33%), significantly improved to a level of 15 dB in one (11%), and unchanged in two (22%). Both these two patients who failed to benefit from MVD had had tinnitus for 6 years and had only a transient relief (for 10 days) after the MVD operation.

More recently imaging techniques have been used. Imaging techniques have the disadvantage that they are directed to morphological features and not function, and it is known that blood vessels in close contact with cranial nerves is common (Sunderland, 1948) while symptoms are rare. That means that diagnosis of disorders that can be cured by MVD operations using imaging techniques have many false positive results.

These studies where the participants had MVD operations had the possibility of visual verification of the presence of a blood vessel in contact with the auditory nerve during the operations but such information is not always included in the published articles. A study of the effectiveness of carbamazepine (Levine, 2006) mentioned that the patients who responded favorably to treatment with carbamazepine also had vascular compression of their auditory nerve as seen on MRI scan.

Discussion

MVD for severe tinnitus can provide benefit to few patients but selection of the patients for the operation is critical. Since the transition between peripheral and central parts of the auditory nerve is located inside the internal auditory meatus the intracranial portion of the nerve is very fragile making the risk of injury to the auditory nerve noticeable.

Abbreviations

ABR	auditory brainstem responses
CT	computed tomography
DPV	disabling positional vertigo
HFS	hemifacial spasm
MRI	magnetic resonance imaging
MVD	microvascular decompression
TGN	trigeminal neuralgia

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CHAPTER 39

Tinnitus in vascular conflict of the eighth cranial nerve: a surgical pathophysiological approach to ABR changes

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Abstract: Some forms of tinnitus are associated with a blood vessel being in close contact with the auditory nerve near its entrance into the brainstem. The outcome of operations for tinnitus, moving the blood vessel off the nerve (microvascular decompression operations, MVD) is less successful than microvascular decompression operations for other vascular conflict syndromes (hemifacial spasm, HFS, and trigeminal neuralgia, TGN). No generally accepted criteria exist for the selection of candidates for MVD for tinnitus. A pathophysiological approach for interpreting auditory brainstem response (ABR) changes is proposed as a basis for selection of tinnitus patients for the MVD operation. We followed changes in the ABR and the tinnitus in 78 patients with unilateral tinnitus, who had indications of having vascular conflicts of the eighth nerve. In 18 of these patients a blood vessel was removed of the auditory nerve and in 9 of these a correlation could be made between preoperative and postoperative clinical changes and ABR changes. In this retrospective study we found abnormalities in the amplitude of peak II and the interpeak latency (IPL) I-III of the ABR that were related to the duration of their tinnitus and its intensity. While no ABR changes could be detected during the first 2 years, after that period a decrease of the amplitude of peak II occurred, and a prolongation the IPL of peak I-III occurred in patients whose peak II had disappeared. The rate of IPL I-III increase slows down after 10 years. IPL I-III prolongation correlates with ipsilateral hearing loss at tinnitus frequency and worsens in time. This correlates with a worsening of the tinnitus associated with the worsening of the IPL I-III. Tinnitus frequency correlates to the frequency of maximal hearing loss and the more the hearing loss at tinnitus frequency the worse the tinnitus. Postoperative improvement of tinnitus correlated with postoperative improvement of peak II and postoperative improvement of hearing loss at the tinnitus frequency correlated with postoperative IPL I-III improvement. It is concluded that interpreting ABRs from a pathophysiological point of view can be beneficial for surgeons performing MVDs for tinnitus, especially with regard to timing of the surgery and interpretation of symptom presentation.

Keywords: ABR; vascular conflict syndrome; auditory nerve; microvascular conflict; tinnitus; pathophysiology

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Introduction

A blood vessel in close contact with a cranial nerve [neurovascular conflict (Sindou et al., 2002)¹] may stimulate axons of the nerve leading to a hyperactive cranial nerve syndrome (Jannetta, 1975; Møller, 1991, 1993a) with or without a loss of function, best known from hemifacial spasm. Microvascular conflict disorders of the fifth and seventh cranial nerves (trigeminal neuralgia, TGN, and hemifacial spasm, HFS) and the vestibular nerve (disabling positional vertigo, DPV) can be diagnosed almost solely on the basis of the patient's history. MRI- and ENT-examinations are used for exclusion of other pathologies and as a possible confirmation of the diagnosis (Møller, 2005).

A cranial nerve has two segments, a central nervous system segment and a peripheral nervous system segment separated by a transition zone (Henschen, 1915, Skinner, 1931) also known as the root entry or root exit zone (for sensory and motor nerves, respectively) or Obersteiner Redlich zone (Obersteiner and Redlich, 1894). The length of the central nervous system (CNS) segment is different in every cranial nerve, with sensory fibers in general having a longer CNS segment than motor fibers of the cranial nerves (Skinner, 1931; Hamlyn, 1999). For the eighth cranial nerve the central segment encompasses the entire cisternal trajectory of the nerve, with the root entry zone located inside or near the entrance of the internal auditory canal (Henschen, 1915). It has been suggested that for a vascular conflict to become symptomatic, the vascular conflict should preferentially be located at the structurally weaker central nervous system segment of the affected cranial nerve (De Ridder et al., 2002).

¹Different investigators have used different terminology regarding the role of blood vessels being in contact with the roots of cranial nerves. The term vascular (or microvascular) compression has been in general use because it was assumed that it was the (pulsatile) pressure from an artery that caused the problems. However, it has become evident that it is not the physical compression that causes the problems but it seems to be the mere contact with a blood vessel (artery or vein) that affects the nerve and subsequently causes the symptoms. We have therefore chosen to use the term vascular (or microvascular) conflict where investigators earlier used the term vascular compression.

Vascular conflicts, when present, are usually unilateral and therefore induce unilateral pathology (Møller et al., 1993b; Fukushima, 1995; Resnick et al., 1995; Lovely and Jannetta, 1997; Kobata et al., 1998). Microvascular conflict disorders are characterized by paroxysmal and intermittent spells of hyperactivity of the cranial nerve involved with a typical evolution: the paroxysms become more frequent over time, the intermittent symptom-free periods become shorter and may develop into a constant dysfunction (Ehni and Woltman, 1945; Ryu et al., 1998; Burchiel and Slavin, 2000). Usually symptoms and signs of vascular conflict disorders can be evoked by specific triggers (Ehni and Woltman, 1945; Resnick et al., 1995; Ryu et al., 1998; Burchiel and Slavin, 2000). The incidence of these disorders increases with age and it is different in men and women (Hamlyn, 1999). Based on the analogy with other vascular conflict syndromes, tinnitus resulting from a vascular contact with the auditory part of the eighth cranial nerve would be expected to present with unilateral tinnitus — presenting as intermittent tinnitus with intervals without tinnitus. Over time the intervals without tinnitus would become progressively shorter, ending in constant tinnitus. While this is the typical course in HFS and TGN (Møller et al., 1986, 1993b) it is not as clear in tinnitus. Also, since tinnitus has so many different forms it is more difficult to identify typical patterns of symptoms than for disorders such as HFS and TGN.

Since also the vestibular part of the eighth cranial nerve might be affected by the same vessel as is in contact with the auditory part of the nerve, optokinetically induced short spells of vertigo could be expected to occur together with tinnitus that is caused by vascular contact with the auditory nerve (Møller, 1990). A disorder known as DPV (Møller et al., 1986) has a similar course as TGN and HFS, with progressively more vertiginous spells and shorter symptom-free periods (Møller, 1990; Møller et al., 1993b; Ryu et al., 1998), and it can be cured by MVD of the vestibular nerve with similar or slightly lower success rate than what is achieved by MVD for HFS and TGN (Møller et al., 1993b). In contrast to Ménière's disease, the spells are shorter lasting and have no aura and no

postictal period. Furthermore, in Ménière's disease there is no auditory brainstem responses (ABR) abnormalities in peak II and IPL I-III (Møller, 1988). Even with these differences, however, confusion between the two entities remains and in one study up to 73% of the patients with successfully treated vascular conflict of the vestibular nerve were diagnosed preoperatively as having Ménière's disease (Ryu et al., 1998). In a chronic stage, vascular conflict of the vestibular nerve induces persistent instability (Schwaber and Hall, 1992; Møller et al., 1993b).

The intermediate nerve and the facial nerve are anatomically located in close relationship to the eighth cranial nerve. Vascular conflict of the central nervous system segment of the intermediate nerve by the same blood vessel can cause bouts of otalgia (deep ear pain), lasting only for seconds. This is also known as geniculate neuralgia (Lovely and Jannetta, 1997). In a later, more chronic stage nervus intermedius conflict becomes associated with a constant deep prosopalgia (pain in the face) (Lovely and Jannetta, 1997). This is in analogy with DPV where in a later stage vertiginous spells become associated with a constant feeling of instability (Schwaber and Whetsell, 1992).

Compression at the CNS segment or the root exit zone of the facial nerve, which lies in very close approximation to the eighth cranial nerve, can result in overt or cryptogenic HFS. Due to the tonotopic organization of the auditory nerve, HFS is usually associated with low-frequency hearing loss and low-frequency tinnitus (Møller and Møller, 1985; De Ridder et al., 2004).

In the present chapter, we describe the results of a study of the changes in the ABR that occur over time and we use this information to help understand the pathophysiology of the forms of tinnitus where vascular conflict is involved. Better understanding of the pathophysiology of this kind of tinnitus would benefit surgeons performing microvascular decompression operations for tinnitus.

The abovementioned description of the symptoms associated with compressions of the four nerves lying in close relationship to each other can be used to create a research classification of increasing certainty of the diagnosis of a cochleovestibular compression (better word is conflict)

syndrome (CVCS) as the cause of tinnitus. The CVCS as cause can only be withheld after all other possible causes of tinnitus are excluded by an ENT specialist, specialised in tinnitus. The classification is predominantly clinically and depends on the presence of unilateral tinnitus and associated symptoms, as well as on morphological (MRI) and neurophysiological (ABR) data. The following selection criteria can be used for this working classification.

1. Intermittent paroxysmal spells of unilateral tinnitus lasting only seconds
2. Associated ipsilateral symptoms
 - a. cryptogenic or overt HFSs
 - b. otalgia with or without deep prosopalgia or feeling of pressure in the ear
 - c. vertiginous spells: short lasting, optokinetically induced
 - d. ipsilateral hearing loss at tinnitus frequency
3. Positive MRI for vascular conflict
4. Positive brainstem auditory evoked potential, using Møller's criteria (Table 1).

These selection criteria can then be classified in four different groups similarly to the AAO-HNS CHE criteria of Ménière's disease (CHE, 1995; Beasley and Jones, 1996) and Poser's criteria for diagnosing multiple sclerosis (Poser et al., 1983), relating to the certainty of the diagnosis of CVCS as the cause of tinnitus.

Possible CVCS: initially intermittent unilateral tinnitus spells without associated symptoms.

Probable CVCS: possible CVCS with associated symptoms (otalgia, vertigo or HFSs) or MRI demonstrating vascular compression of cochleovestibular nerve (using high resolution

Table 1. Møller's ABR criteria for diagnosing a microvascular conflict of the eighth nerve (Møller, 1990)

Ipsilateral IPL I-III ≥ 2.3 ms
Contralateral IPL III-V ≥ 2.2 ms
IPL I-III difference ≥ 0.2 ms
IPL III-V difference ≥ 0.2 ms
IPL I-III difference ≥ 0.16 ms if low or absent peak II
IPL III-V difference ≥ 0.16 ms if low or absent peak II
Peak II amplitude $< 33\%$

heavily T2 weighted CISS images) or abnormal ABR.

Definite CVCS: probable CVCS with associated symptoms and/or abnormal ABR and/or abnormal MRI.

Certain CVCS: definite CVCS which is surgically proven.

Materials and methods

Seventy-eight individuals with symptoms suggestive of eighth nerve vascular conflict (tinnitus that was referred to one ear) (possible CVCS) were included in this study (Table 2).

Some parts of this study are based on retrospective file research. The postoperative data were collected in a prospective design. In the retrospective part, not all the clinical parameters were available. This is the reason why the group sizes vary slightly among different statistical tests. Participants who presented at the multidisciplinary tinnitus clinic of the Antwerp University Hospital, Belgium underwent a standardized protocol consisting of clinical ENT examination, pure tone audiometry, ABR, tympanometry, tinnitus matching

and 1.5T MRI using heavily T2 weighted images (constructive interference in steady state, CISS), with 0.6 mm slice thickness. However some patients presented with ABRs being performed at other departments. These data were excluded from data processing in the retrospective analysis for methodological reasons.

The participants were divided in three different groups, based on the abovementioned classification with increasing likelihood of eighth nerve vascular conflict being the cause of tinnitus. After exclusion of other pathologies as the cause for tinnitus, 78 participants were entered into the possible group. Fifty-one participants demonstrated associated clinical symptoms as mentioned before, such as cryptogenic HFS, otalgia, optokinetic vertigo, hearing loss at tinnitus frequency or a positive vascular conflict on MRI. These 51 participants were classified into the probable group. Within this probable group, 21 participants revealed both associated clinical symptoms and a positive MRI, and these participants were assigned into the definite group. Eighteen participants were operated on and in all of them a vascular conflict was confirmed. These belong to the certain group.

The tinnitus intensity severity was analyzed using a visual analog scale. The severity of tinnitus distress was analyzed using a validated tinnitus questionnaire (Goebel and Hiller, 1994). This questionnaire consists of 52 questions that are scored and result into a total score which classifies the participant in one of the four grades: grade 1, mild tinnitus; grade 2, moderate tinnitus; grade 3, severe but compensated tinnitus; grade 4, severe and (psychologically) decompensated tinnitus.

The ABRs elicited by clicks with alternating polarity were obtained with a Nicolet Viking IV D system. The stimuli were presented through headphones at a rate of 16.0 clicks/s. The stimulus intensity was 80 dB HL but a few were 90 dB or 100 dBnHL, which was proportional to the participants hearing loss. Noise was presented to the opposite ear at a sound pressure level that was 40 dB below that of the clicks. The ABR was recorded from electrodes placed on the vertex and the mastoid using filter settings at 150–1500 Hz. At each stimulus condition two runs of 2000 responses was averaged and digitally filtered to

Table 2. Demographic data

Demographic data		
Possible	Cases 78	
	Men 45	Women 33
	Left 37	Right 41
	Age range 25–73 years (mean 51.37)	
	Duration of illness 0.5–56 years (mean 6.79)	
Probable	Cases 51	
	Men 29	Women 22
	Left 26	Right 25
	Age range 25–73 years (mean 50.11)	
	Duration of illness 1–56 years (mean 6.45)	
Definite	Cases 21	
	Men 10	Women 11
	Left 9	Right 12
	Age range 26–73 years (mean 48.20)	
	Duration of illness 1–25 years (mean 5.15)	

enhance the peaks of the ABR. Computer programs were used to automatically identify the different peaks and to print the latencies of the peaks.

Pre-and postoperative ABR and clinical data were available for 9 of the 18 operated participants whose tinnitus or hearing changed after moving a blood vessel off the eighth nerve. If neither hearing nor tinnitus changed after decompression the operated participants were excluded from further analysis. A separate analysis is performed on these participants correlating the tinnitus changes and frequency-specific hearing threshold changes at tinnitus frequency to ABR changes of peak II and IPL I-III. This is done using a pre/postop peak II ratio = (postop ipsilateral peak II ampl/postop contralateral peak II ampl)/(preop ipsilateral peak II ampl/preop contralateral peak II ampl) and pre/postop IPLI-III difference = postop IPL I-III — preop IPL I-III.

All collected information was entered in a Microsoft Access 2003 database and statistical analysis was performed using SPSS 13.0 for Windows. The relation between age and IPL I-III (used to age-normalize IPL I-III: AN IPL I-III), tinnitus duration versus AN IPL I-III, hearing loss versus IPL I-III and finally ipsilateral IPL I-III versus contralateral IPL I-III were investigated with Pearson's correlation coefficient. Correlations with tinnitus duration or age were, when relevant, examined with linear regression. All correlations with tinnitus severity were performed using Spearman's rho. Student's independent samples T-test was used to analyze the difference of ipsilateral AN IPL I-III in peak II presence or absence, contralateral AN IPL I-III in presence or absence of peak II and hearing loss in presence or absence of peak II. Chi-square was utilized to relate ipsilateral peak II presence/absence to contralateral peak II presence/absence. Spearman's rho was used to investigate the variable correlations of the pre- and postoperative data. Significance was reached when $p < 0.05$.

Results

The IPL I-III of the ABR was positively correlated with the participants' age. Taking this into account, IPL I-III was normalized to the

participants' age. After removing two outliers the Pearson correlation coefficient between contralateral IPL I-III (= normal ears) and age was 0.490 ($n = 28$; $p = 0.008$). The calculated linear regression was 8.510×10^{-3} ms/year and this value was used to normalize the IPL I-III to age (normalized IPL I-III = IPL I-III—age $\times 8.510 \times 10^{-3}$).

Hearing loss at the frequency of the tinnitus was weakly correlated but there was a significant correlation between hearing loss and the ipsilateral IPL I-III ($n = 55$, $r = 0.268$, $p = 0.048$), but no significant correlation with contralateral IPL I-III was found ($n = 60$, $r = 0.074$, $p = 0.574$).

The presence of the ipsilateral peak II was correlated with the presence of the contralateral peak II in the possible group, whereas no correlation can be found between the presence of the contralateral peak II for the probable and definite group (Table 3). This suggests that in the groups of higher diagnostic certainty (probable and definite group) peak II abnormalities were real abnormalities.

Participants with peak II absence have a significantly higher maximum hearing loss on any of the audiogram frequencies than participants with peak II presence in both the possible and the probable group (Fig. 1).

It is also nearly significant in the definite group (Table 4). The tinnitus is of the same frequency as the maximum hearing loss (possible eighth nerve vascular conflict: $n = 65$, $\text{corr} = 0.379$, $p < 0.002$; probable $n = 40$, $\text{corr} = 0.456$, $p < 0.003$; definite $n = 16$, $\text{corr} = 0.690$, $p < 0.003$). Furthermore the hearing loss at the tinnitus frequency correlates highly with the tinnitus severity (definite $n = 16$, $\text{corr} = 0.750$, $p = 0.001$) (Fig. 2).

In the operated participants, peak II recovery postoperatively correlates with the improvement of tinnitus postoperatively $n = 9$; $rs = -0.714$;

Table 3. χ^2 analysis of ipsilateral and contralateral peak II presence

	df	χ^2	Probability
Possible	1	6.300	0.012*
Probable	1	3.396	0.065
Definite	1	1.371	0.242

* $p < 0.05$

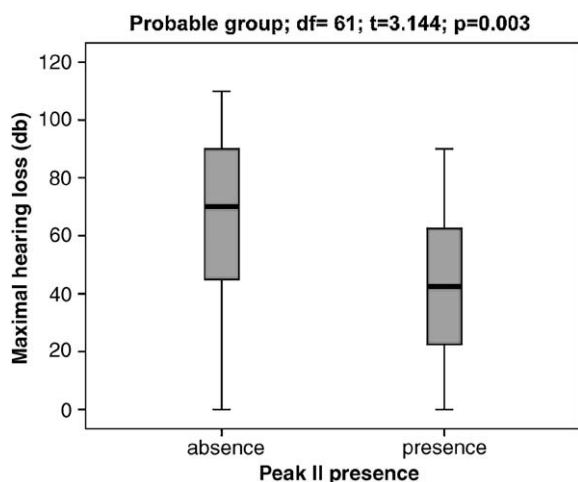


Fig. 1. Correlation between the absence of peak II of the ABR and hearing loss in the probable group. Absence of peak II signifies a dysfunctional nerve conduction in the cisternal (= CNS) segment of the auditory nerve, and correlates to the amount of hearing loss ($df = 61$; $t = 3.144$; $p = 0.003$).

Table 4. Student-*t* analysis of hearing loss and peak II relation

	df	<i>t</i>	Probability
Possible	93	2.265	0.026*
Probable	61	3.144	0.003*
Definite	21	1.949	0.065

* $p < 0.05$

$p = 0.031$ (Spearman), but not to frequency-specific hearing improvement at the tinnitus frequency (Fig. 3).

In the operated participants, the recovery of the IPL I-III postoperatively correlates to the improvement of hearing loss at the tinnitus frequency postoperatively $n = 9$; $rs = 0.857$; $p = 0.003$ (Spearman), but not to tinnitus improvement (Fig. 4).

A correlation exists between the presence of peak II and the IPL I-III prolongation in the definite group. If peak II is not present the IPL I-III prolongs ($df = 21$; $t = 2.702$; $p = 0.013$). See Fig. 5 and Table 5. This is not found when peak II is compared to the contralateral age normalized IPL I-III. A significant correlation exists between the IPL I-III prolongation and the tinnitus severity (Table 6).

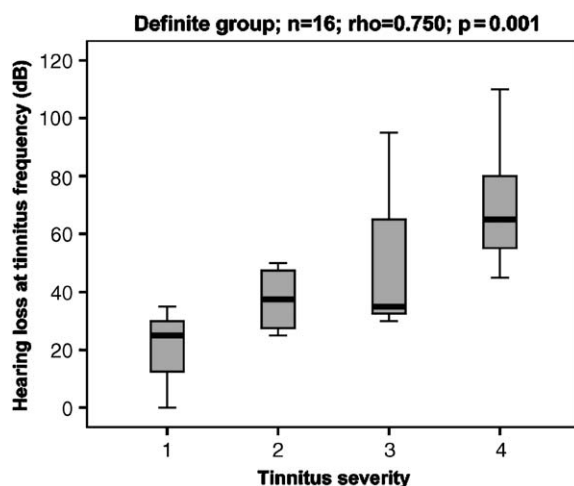


Fig. 2. Correlation between hearing loss at tinnitus frequency and tinnitus degree in definite group ($n = 16$, $\rho = 0.750$, $p = 0.001$). The higher the hearing loss at the tinnitus frequency, the worse the tinnitus is perceived.

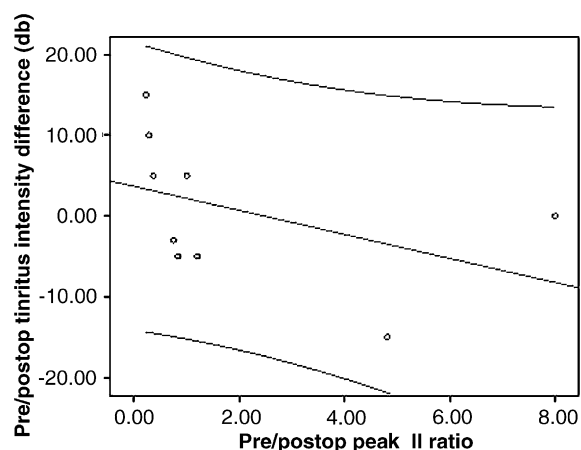


Fig. 3. Relation between pre and postop peak II ratio and pre and postop tinnitus intensity difference (dB) [$n = 9$; $rs = -0.714$; $p = 0.031$ (Spearman)].

A correlation can be found between IPL I-III and the tinnitus duration after normalization for age in the probable group (probable $n = 16$, $r = 0.501$, $p = 0.048$) (Fig. 6 and Table 7). The longer the tinnitus exists, the more the auditory nerve becomes damaged. In participants having tinnitus longer than 10 years, the age-normalized IPL I-III correlation correlates with tinnitus

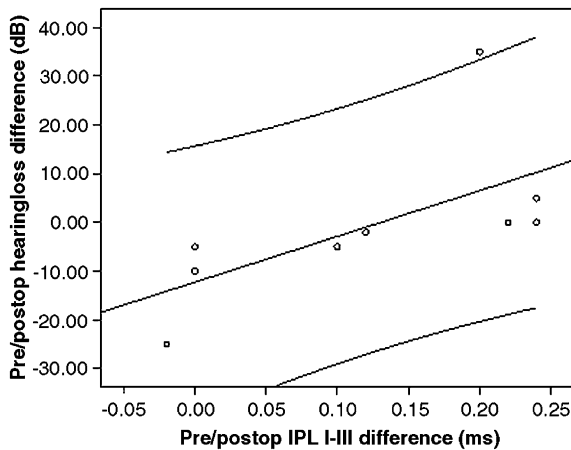


Fig. 4. Relation between pre and postop IPL I-III difference and pre and postop hearing loss difference (dB) [$n = 9$; $r_s = 0.857$; $p = 0.003$ (Spearman)].

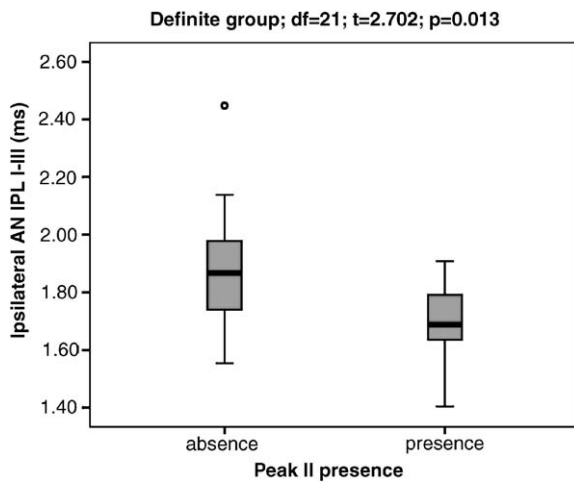


Fig. 5. Relation between the presence of peak II and the IPL I-III prolongation in the definite group. If peak II is not present the IPL I-III prolongs ($df = 21$; $t = 2.702$; $p = 0.013$).

duration for both the probable and definite groups (Table 7). The prolongation of the age-normalized IPL I-III overall in participants with tinnitus presenting for more than 2 years was statistically significantly related to the duration of the tinnitus in all groups. On the other hand there was no significant correlation between the tinnitus duration and the contralateral age-normalized IPL I-III for participants who had unilateral tinnitus for more than 2 years.

Table 5. Student- t analysis of peak II and ipsilateral AN IPL I-III

	df	t	Probability
Possible	57	1.172	0.246
Probable	45	1.683	0.099
Definite	19	3.606	0.002*

* $p < 0.05$

Table 6. Spearman's rho correlation between AN IPL I-III and tinnitus severity

Group	Cases	Correlation	Probability
Possible	42	0.231	0.142
Probable	17	0.782	0.001
Definite	9	0.811	0.008

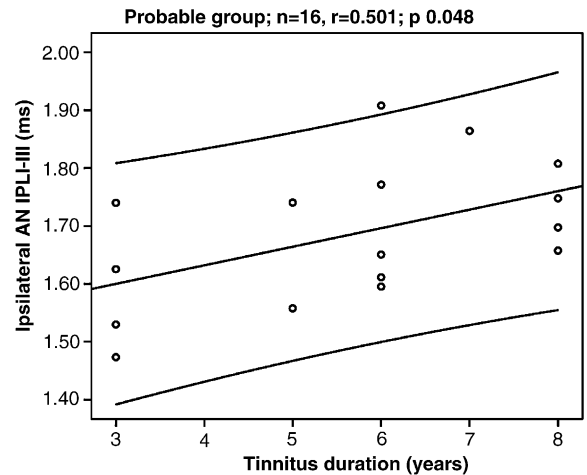


Fig. 6. Correlation between IPL I-III and the tinnitus duration after normalization for age in the probable group (probable $n = 16$, $r = 0.501$, $p = 0.048$). This suggests that the longer the tinnitus exists, the more the auditory nerve becomes damaged.

Regression analysis revealed that ipsilateral age-normalized IPL I-III increased at a rate of 32.02×10^{-3} ms/year for participants having tinnitus between 2 and 10 years in the probable group, and 6.616×10^{-3} ms/year for participants having tinnitus for more than 10 years.

A correlation exists between the AN IPL I-III and the tinnitus grade for the probable group and definite group (Table 7), except for grade 4. The more the damage to the auditory nerve the worse the tinnitus (Fig. 7).

Table 7. Pearson correlation of ipsilateral AN IPL I-III and tinnitus duration

	Group	Cases	Correlation	Probability
<2 Years	Possible	36	-0.193	0.258
	Probable	25	-0.056	0.792
	Definite	12	-0.088	0.787
>2 Years	Possible	42	0.375	0.014*
	Probable	26	0.435	0.026*
	Definite	9	0.703	0.035*
2-10 Years	Possible	27	0.278	0.161
	Probable	16	0.537	0.032*
	Definite	4	0.105	0.895
>10 Years	Possible	15	0.653	0.008*
	Probable	10	0.886	0.001*
	Definite	5	1000	<0.001*

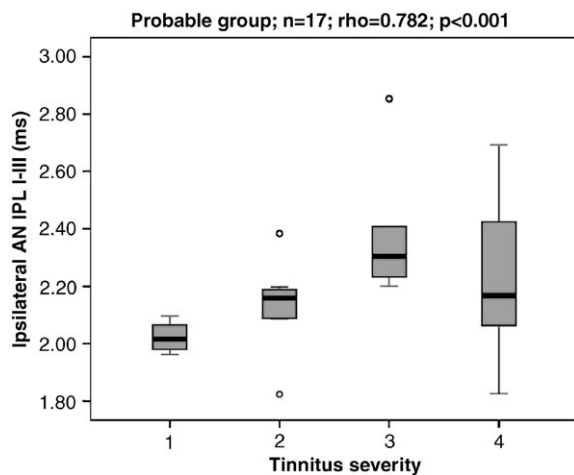
* $p < 0.05$ 

Fig. 7. Relation between the AN IPL I-III and the tinnitus grade for the probable group (probable: $n = 17$, $\rho = 0.782$, $p < 0.001$) except for grade 4. The more the damage to the auditory nerve, the worse the tinnitus. A possible reason why grade 4 tinnitus (= decompensated tinnitus) might be not following this tendency could be because these participants are psychologically decompensated.

Discussion

Many investigators have presented hypotheses about the pathophysiology of microvascular conflict disorders that were based on demyelination of axons at the location of the vascular contact (Møller, 1984; Nielsen, 1984; Kuroki and Møller,

1994; Love and Coakham, 2001; Devor et al., 2002). Our postoperative results however suggest that the tinnitus might not be the result of such suggested demyelination as IPL I-III is uncorrelated to the tinnitus, but that focal signal transmission changes are causing the tinnitus. In other words the irritation of the auditory nerve from close contact with a blood vessel may lead to reorganization of auditory nuclei in the auditory brainstem probably induced by the expression of neural plasticity (Møller, 2006b, c). This neural plasticity may affect the entire auditory pathways including the auditory cortex causing re-organization (Mühlnickel et al., 1998) and creating hyperactivity in the auditory cortex, which may be clinically expressed as tinnitus (De Ridder et al., 2004).

It has been suggested that a vascular conflict, in order to become symptomatic, should be located at the CNS segment (and not just the root entry zone), which is the neural generator of peak II. Thus peak II changes are expected to be the first abnormality to be noted in vascular conflicts of the auditory nerve. Evoked potentials are the result of a synchronized firing pattern as a reaction to a sensory stimulus (Møller, 2006a). The more synchronized the nerves fire the higher the amplitude of the evoked potentials will be. The contact with a blood vessel may alter neural conduction (decrease conduction velocity in some fibers or inactivate some fibers) causing the temporal coherence of the firing in the central segment of the auditory nerve to decrease, resulting in a decrease of the amplitude of peak II, and clinically this may result in frequency-specific tinnitus (Fig. 1).

This conflict seems to induce a progressive pathology. The fact that IPL I-III increases arise when peak II is absent (Fig. 5) and that IPL I-III prolongs in time (Fig. 6) suggests that in time the blood vessel not only induces a signal transmission disruption (peak II decrease) but also induces a slowing down of signal transmission, and that this is progressive i.e. it worsens in time. This slowing down of signal transmission in the auditory nerve could be due to a focal demyelination (Waxman, 1977). Our data demonstrate that only the ipsilateral IPL I-III prolongation is correlated to hearing loss at the frequency of the tinnitus but not so the

contralateral IPL I-III. This suggests that hearing loss in this population is indeed most likely due to the vascular conflict and not to other factors such as age. As the auditory nerve has a tonotopic structure (Sando, 1965; De Ridder et al., 2004), the site of the conflict is likely to cause a frequency-specific change in function of the auditory nerve, i.e. a frequency-specific hearing loss and a frequency-specific tinnitus (De Ridder et al., 2004; Nowe et al., 2004). Our data confirm this. The hearing loss that develops in MVC of the eighth cranial nerve is maximal at the tinnitus frequency.

The study also shows that the prolongation of IPL I-III is related to the severity of the tinnitus degree (Fig. 7). This correlation between IPL I-III prolongation and tinnitus severity was not present in the participants who had tinnitus grade 4, most likely due to the fact that these participants probably have a considerable psychological overlay and that they perceive and thus score their tinnitus worse than the participants who had the same tinnitus but who did not have such a similar psychological overlay.

The fact that worsening of frequency-specific hearing loss is associated with progressive increase in tinnitus (Fig. 2) and that IPL I-III prolongation relate in a statistically significant way to the tinnitus degree (Fig. 7) suggests that the more the auditory nerve becomes damaged, the worse the tinnitus becomes.

Furthermore our postoperative changes in the ABR suggest that IPL I-III is causally related to hearing loss at the tinnitus frequency, as the hearing loss at tinnitus frequency improves when the IPL I-III improves. Thus when signal transmission improves, i.e. when the auditory nerve recovers, hearing loss at the tinnitus frequency improves.

It is not clear why the shortening (normalization) of the IPL I-III is not associated with an improvement of the tinnitus as well. This may be taken as a sign of the complexity of the pathology of tinnitus, involving not only morphological changes but also factors such as expression of neural plasticity which play a role in the pathology of tinnitus (Møller, 2006b) (see Chapter 3).

Thus, whereas tinnitus most likely develops as a result of irritation of the auditory nerve in an initial stage, corresponding to a decrease in

peak II, at a later stage it might be the result of a frequency-specific hearing loss, corresponding to IPL I-III prolongation, due to focal demyelination (Fig. 8). At this stage the tinnitus might be caused by auditory deprivation, rather than mere irritation. This explains why the tinnitus frequency in these patients is the same frequency as that of maximal hearing loss.

The results of the present study will benefit surgeons involved in microvascular decompression surgery for tinnitus. The results of the present study provide some explanation to other findings that have shown that participants who have had tinnitus for a long time have less benefit from microvascular decompression operations than

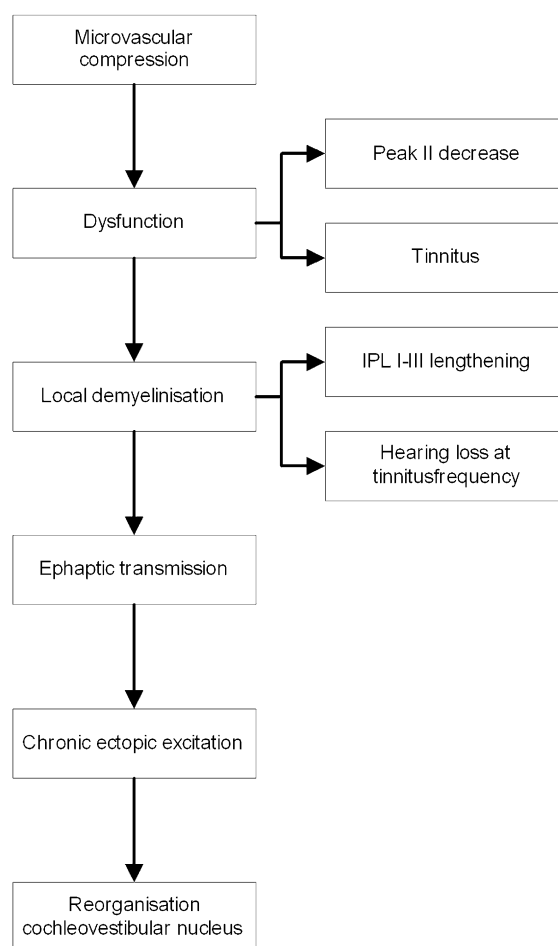


Fig. 8. A pathophysiological model of microvascular conflicts of the auditory nerve based on ABR changes.

participants who have had tinnitus for a short period (see Chapter 38) (Møller et al., 1993a) and similarly when the tinnitus is associated with a hearing loss (Ryu et al., 1998).

A typical history of unilateral intermittent tinnitus, associated with short bouts of optokinetic vertigo, and/or ipsilateral short spells of otalgia and/or ipsilateral overt or cryptogenic HFSs are suggestive of an MVC being the cause of the tinnitus. A positive compression seen on MRI and an ipsilateral peak 2 decrease on ABR increase the likelihood of the diagnosis. But, based on these results it can be suggested that MVD operations should be performed before IPL I-III becomes prolonged, as this might be a sign of irreversible damage.

Conclusion

Vascular conflict of the eighth cranial nerve is accompanied by a sequential pattern of ABR changes. The first 2 years, no noticeable ABR changes occur, but after that the amplitude of the ipsilateral peak II decreases and the ipsilateral IPL I-III becomes prolonged. As the tinnitus generation at an early stage might be due to mere neuronal irritation and at a later stage due to possibly irreversible sensory deprivation microvascular decompressions should be performed at an early stage, before IPL I-III prolongation occurs. An ipsilateral peak II decrease could be used as a neurophysiological sign of tinnitus in this setting.

Abbreviations

AAO-HNS	American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium
ABR	auditory brainstem responses
AN	age normalized
CISS	constructive interference in steady state
CNS	central nervous system
CVCS	cochleovestibular compression syndrome or cochleovestibular conflict syndrome

dB	decibel
DPV	disabling positional vertigo
ENT	ear, nose and throat
HFS	hemifacial spasm
HL	hearing level
Hz	herz
IPL	interpeak latency
MRI	magnetic resonance imaging
MVC	microvascular compression or microvascular conflict
MVD	microvascular decompression
T	tesla
TGN	trigeminal neuralgia

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CHAPTER 40

Tinnitus retraining therapy

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Abstract: Tinnitus retraining therapy (TRT) is a specific clinical method based on the neurophysiological model of tinnitus described by Jastreboff (Jastreboff, P.J. (1990). *Neurosci. Res.*, 8: 221–254). The method is aimed at habituation of reactions evoked by tinnitus, and subsequently habituation of the tinnitus perception. Several other methods have been suggested for habituation of tinnitus, but in TRT two components that strictly follow the principles of the neurophysiological model of tinnitus are implemented and necessary: (1) counseling, aimed at reclassification of tinnitus to a category of a neutral signals and (2) sound therapy, aimed at weakening tinnitus-related neuronal activity as suggested by Jastreboff and Hazell (Jastreboff, P.J. and Hazell, J.W.P. (2004). Cambridge University Press, Cambridge). This chapter outlines the theoretical basis of TRT as well as comments on the clinical outcome of the use of TRT for different kinds of tinnitus.

Keywords: tinnitus retraining therapy; learning; conditioned reflexes; conscious and subconscious paths; the limbic and autonomic nervous systems

Introduction

The neurophysiological model of tinnitus

The main postulate of the neurophysiological model (Jastreboff, 1990) of tinnitus is that other systems in the brain, in addition to the auditory system, have to be involved in the clinically significant tinnitus, i.e., tinnitus which bothers people to such an extent that it interferes with their everyday life. Moreover, these systems, specifically the limbic and sympathetic part of the autonomic nervous systems, are actually responsible for negative, bothersome reactions to tinnitus (Jastreboff and Hazell, 2004).

The second postulate, that tinnitus is a phantom auditory perception (Jastreboff, 1990), is currently

accepted by a majority of investigators and clinicians (Muhlneckel et al., 1998; Möller, 2003, 2006; Eggermont and Roberts, 2004; Muhlau et al., 2006; Bartels et al., 2007; Weisz et al., 2007) and has many significant consequences. It points out that tinnitus perception results from the detection and perception of neuronal activity within the auditory pathways — similarly to perception of activity evoked by a sound, but in the case of tinnitus without being linked to any mechanical, vibratory activity present within the cochlea. This is in contrast to what has been labeled as “objective tinnitus” where the perception is caused by physical sounds that are generated in the body. “Objective tinnitus” is currently labeled a “somatosound” (Jastreboff and Jastreboff, 2003). The recognition that in case of tinnitus there is no vibratory activity within cochlea solved a number of tinnitus puzzles. For example, suppression of tinnitus perception reflects neuronal suppression and not

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auditory masking; therefore, there is no clear frequency relation between tinnitus pitch match and frequency of external sound and there is no critical band phenomenon (Feldmann, 1971). The phantom nature of the tinnitus perception explains why on many occasions it is impossible to suppress tinnitus perception even by very high levels of the sound, and why sound levels needed for suppression are higher than predicted from tinnitus loudness match. All these observations have significant implication on all treatments, which utilize sound to interfere with abnormal neural activity that causes the tinnitus, including masking or sound therapy of TRT.

Third postulate of the model differentiate between mechanisms involved in tinnitus perception and in tinnitus-induced suffering (e.g., annoyance, anxiety, problems with sleep and concentration). The mechanisms responsible for generation of tinnitus-related neuronal activity, perceived as tinnitus, are common for people who just experience tinnitus (~80% of all individuals with tinnitus) and those who suffer because of it. This is supported by a lack of differences in psychoacoustical characterization of tinnitus (i.e., its pitch and loudness match and minimal suppression “masking” level) between these two groups of individuals with tinnitus (Jastreboff et al., 1994). Specific mechanisms, which are responsible for spreading tinnitus-related neural activity to other structures in the brain, are present only in people who suffer from their tinnitus and are separate from mechanism involved in generation of the perception of abnormal neural activity that causes the tinnitus. Therefore, these two groups of mechanisms are discussed separately in this chapter.

Many mechanisms have been proposed as being responsible for the generation of abnormal neural activity that causes tinnitus (Kiang et al., 1970; Salvi and Ahroon, 1983; Møller, 1984, 1999; Tonndorf, 1987; Pujol, 1992; Jastreboff, 1995; Eggermont and Roberts, 2004; Eggermont, 2005, 2006; Heinz et al., 2005; Weisz et al., 2005; Ma et al., 2006; Zenner et al., 2006; Mazurek et al., 2006b; Sanchez et al., 2007). While the neurophysiological model of tinnitus does not depend on mechanism responsible for generating the neural activity that causes the perception of tinnitus, a

specific mechanism was proposed together with the model, called discordant damage (dysfunction) of outer and inner hair cell systems (Jastreboff, 1990). This hypothesis has been described previously in detail (Jastreboff and Hazell, 2004) and only an outline is presented here.

Discordant damage of outer and inner hair cells

Inner hair cells (IHC) are the auditory receptor cells that transduce the sound-evoked mechanical vibration in the cochlea into a neural code in auditory nerve fibers and thus subsequently make it possible to perceive sounds. Outer hair cells (OHC) on the other hand are mechanical amplifiers providing 50–60 dB of amplification. OHCs are helpful, but not necessary for hearing and have little effect on sounds louder than ~60 dB HL. OHCs are typically damaged first by ototraumatic events, but even with up to 30% damage to OHCs, the impact on the hearing threshold is minimal (Chen and Fechter, 2003).

The discordant dysfunction theory postulates that each area on the cochlear basilar membrane on which OHC are totally or partially dysfunctional and IHC are in better functional shape than OHC causes an imbalance of activity in the dorsal cochlear nucleus, specifically, disinhibition caused by decreased inhibitory input from OHC (Jastreboff and Hazell, 2004). This in turn may increase spontaneous activity (Kaltenbach, 2006) and result in emergence of bursting, epileptic-like activity, which is further processed within the auditory pathways (Chen and Jastreboff, 1995; Jastreboff, 2004). Currently, the available data support the “discordant dysfunction” theory, including its prediction that increase of the damage to the IHC system with constant level of damage of OHC could actually decrease tinnitus (Kaltenbach et al., 2002; Jastreboff and Hazell, 2004).

The discordant dysfunction theory can explain many observations, which are difficult to explain otherwise. For example, the presence of tinnitus in patients with normal hearing can be due to the presence of patches of dysfunctional OHC, the effect of which cannot be detected by standard audiometric tests (pure tone threshold) but can be

identified by otoacoustic emission testing. This can explain the association of distortion product otoacoustic emission (DPOAE) and tinnitus (Ozimek et al., 2006; Hall, personal communication). Indeed, high frequency resolution DPOAE performed on our patients since 1992 indicate higher extent of irregularity than in the DPOAE of individuals without tinnitus. On the other hand, the absence of tinnitus in 27% of people with total deafness (Hazell et al., 1995) can be explained noticing that the neural activity that causes the tinnitus depends on the difference between functionality of OHC and IHC. If both systems are totally destroyed then the abnormal neural activity that causes tinnitus would be less pronounced than what it would when only OHC are dysfunctional as there would be a smaller difference in activity coming from OHC and IHC systems. Consequently, this signal can easily undergo spontaneous habituation. In the majority of individuals with tinnitus, the pitch of the tinnitus tends to be in the frequency range of the greatest hearing loss. The biggest difference between OHC and IHC functionality is expected to occur in the region of the basilar membrane that is tuned to these frequencies. Typically, cochlear damage along the basilar membrane process through stages of: gradually increase of damage to OHC with little damage to IHC, and damage the IHC only occurs when all OHC are destroyed (Chen and Fechter, 2003). Thus, the frequency range of the greatest hearing loss, particularly the bottom of the slope of audiogram, corresponds to the area of the basilar membrane where the difference between damage of OHC and IHC systems is largest. Hearing loss from exposure to loud noise is an important factor associated with tinnitus (Hoffman and Reed, 2004). Noise exposure causes damage/dysfunction of OHC first and only at very high sound levels does the damage extend to IHC (Chen and Fechter, 2003). Therefore, according to discordant damage theory, noise causes the optimal situation to induce tinnitus. Furthermore, “disco tinnitus,” i.e., temporal tinnitus associated with exposure to loud music can be explained as loud sound causing disorganization of cilia of OHC. Under such situations, these cells are temporarily disabled and if they are not irreversible

damaged, the cilia return to normal state after few hours — days.

Salicylate (aspirin), quinine, and cisplatin are the most powerful drugs to induce tinnitus. Administration of salicylate in high doses always induce tinnitus (Mongan et al., 1973). These drugs, while working through different biochemical mechanisms (see Chapter 12), all mostly affect OHC with little or no effect on the function of IHC.

There are many other potential mechanisms of inducing abnormal neural activity that causes the tinnitus, including central tinnitus; however, it seems that discordant dysfunction theory is applicable to majority of individuals with tinnitus and it is useful in patient counseling. Note, that the validity of the neurophysiological model of tinnitus, and consequently TRT, do not depend on the proposed mechanisms generating the abnormal neural activity that causes the tinnitus.

Physiologic aspects of suffering from tinnitus

The hypothesis proposed in the neurophysiological model of tinnitus that the mechanisms of tinnitus-induced problems (e.g., annoyance, anxiety, panic, sleep, and concentration disturbances) involve other than auditory system emerged from analysis of clinical information. There is a difference between experiencing tinnitus and suffering from tinnitus. Tinnitus is bothersome for only ~20% of people experiencing tinnitus (Coles, 1996; Davis and El Refaie, 2000; Hoffman and Reed, 2004). There are no known differences in its pitch, matching of its loudness and the ability to mask the tinnitus with sounds of tinnitus that does not cause suffering and tinnitus that cause suffering. If auditory system was crucial in determining the extent of tinnitus-induced problems, the psychoacoustic of tinnitus should play a dominant role. It has also been observed that the severity of tinnitus and treatment outcome do not depend on the psychoacoustical characteristic of the tinnitus (Jastreboff et al., 1994). This observation argues against the auditory system being the anatomical location where aspects of tinnitus that leads to suffering are processed and interpreted. If the auditory nervous

system was the location where such aspects of tinnitus were processed it could be predicted that louder tinnitus would be more bothersome and more difficult to treat than softer tinnitus.

Finally, audiologic data show that average hearing is the same for the tinnitus and nontinnitus population (Jastreboff and Hazell, 2004). A comparison of the hearing thresholds of a population of people attending a tinnitus clinic, and who had bothersome tinnitus, with those from a gender and age matched group of individuals without tinnitus revealed that their hearing loss are essentially identical (Hazell and McKinney, 1996). While the prevalence of tinnitus perception increases with hearing loss, nevertheless occurrence of bothersome tinnitus does not seem to follow such simplistic rules (Hoffman and Reed, 2004).

The lack of relationship between psychoacoustic description of tinnitus and its severity and treatment outcome indicate that the auditory system does not play a primary role in tinnitus that cause suffering (clinically relevant tinnitus) but that non-auditory systems in the brain have a dominating role in creation of such qualities of tinnitus. The model postulated that tinnitus-induced problems (suffering) involved the limbic and autonomic nervous systems (Jastreboff, 1990, 1995). In particular, activation of the sympathetic part of the autonomic nervous systems is important in determining the severity of tinnitus. The limbic system controls emotional expression, memory storage and recall, motivation and mood, and it directly influences neuroendocrine and autonomic functions. The autonomic nervous system controls the action of glands, respiratory, circulatory, digestive, hormonal, and urogenital system (Møller 2003, 2006; Brodal 2004).

Development of tinnitus

Three stages in the development of tinnitus can be identified: (1) generation of the abnormal neural activity that causes the tinnitus; (2) interpretation of the abnormal neural activity; and (3) its perception and evaluation in high regions of the CNS. For clinically significant tinnitus (tinnitus that causes suffering) there is an additional stage (4)

sustained activation of brain regions that are not specifically auditory such as the limbic and autonomic nervous systems.

These steps are illustrated in Figs. 1A–D. Initially, the abnormal neural activity that causes tinnitus is typically generated at the periphery of the auditory system (Fig. 1A), perhaps in the dorsal cochlear nucleus (Jastreboff and Hazell, 2004; Kaltenbach, 2006). This signal may then be detected and further processed in the subconscious part of the brain (Chen and Jastreboff, 1995; Jastreboff, 2004) (Fig. 1B). Finally, it reaches the high cortical levels of the auditory system where it is perceived. Note, that in this idealistic situation other systems in the brain are not activated. Abnormal neural activity that causes the tinnitus is then treated as any other background sound and it is not evoking any reaction. However, under real-life conditions, when tinnitus is perceived as a new signal, it is evaluated, compared with information stored in memory, and attracts attention. Two potential scenarios are then possible. If the abnormal activity that causes tinnitus is classified by the conscious and the subconscious brain as a neutral stimulus, then it is subsequently blocked from reaching conscious perception (habituation of perception) and it is not spreading to other systems in the brain, as there is no need for any action in response to its presence. Specifically, the limbic and autonomic nervous systems are not activated by such neural activity (Fig. 1C). This scenario happens spontaneously in the majority of persons with tinnitus.

If however the abnormal neural activity that causes the tinnitus gets some negative connotation it is classified in the category of potentially unpleasant or even dangerous stimuli and consequently activates the limbic and autonomic nervous systems to assure readiness to reaction in response to its presence and attracts attention forcing its further evaluation (Fig. 1D) and a cascade of events occurs. If a person does not possess sufficient knowledge about the benign nature of tinnitus then, as with all unknown stimuli, the automatic assumption is that it might be something troublesome, attract attention and the process of conscious thinking about it and further analysis starts.

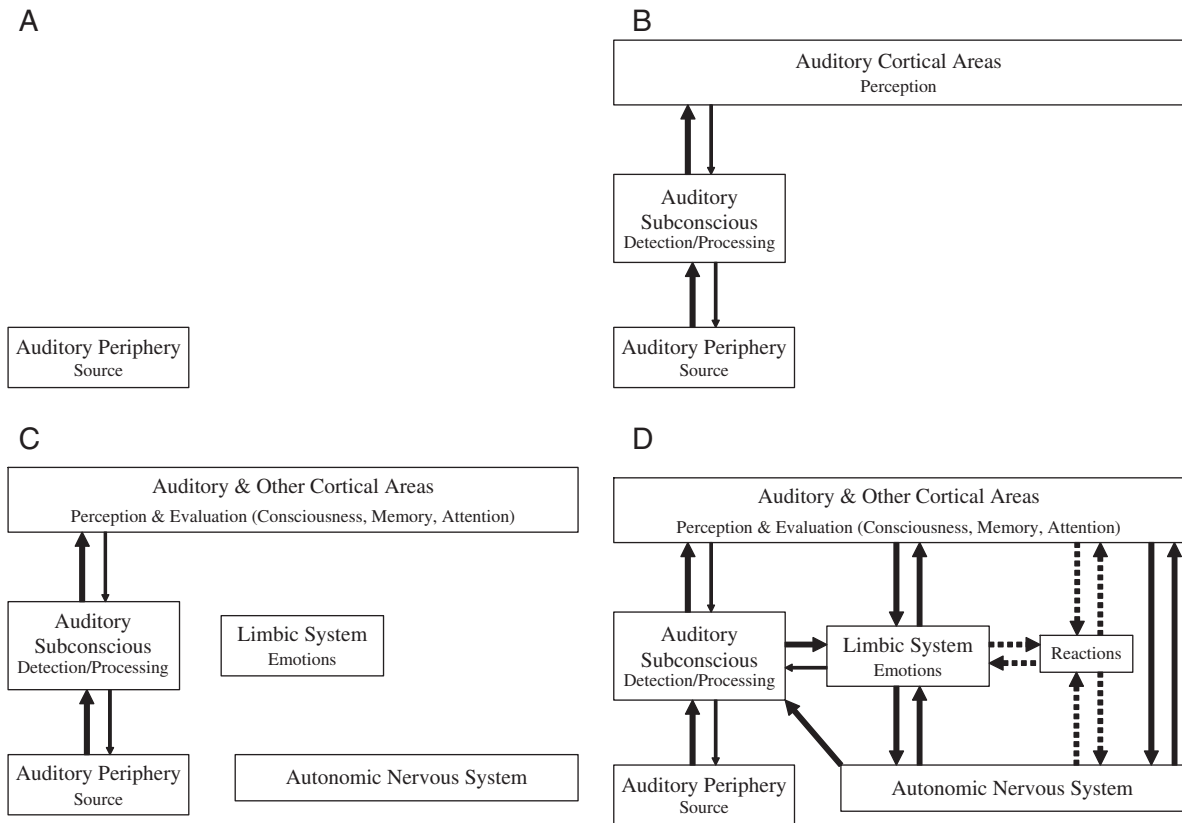


Fig. 1. Development of connections yielding tinnitus-induced negative reactions. (A) First stage, with tinnitus source being typically located in the periphery of the auditory system. (B) The abnormal neural activity that causes tinnitus is detected and processed at subconscious pathways of the auditory system and perceived at auditory cortex. (C) Evaluation of abnormal neural activity that causes the tinnitus as neutral stimulus prevents activation of the limbic and autonomic systems; this is situation in majority of tinnitus cases when spontaneous habituation of tinnitus occurs. (D) Classification of tinnitus as an important, negative stimulus yields development of self-enhancing loops governed by principles of the conditioned reflexes. Note, two loops — high, cortical involving consciousness, and subconscious loop.

Negative reactions induced by tinnitus depend on activation of limbic and the autonomic nervous system, and may be enhanced by prolonged activation of these systems. The fact that the functional connections between auditory system and limbic and autonomic structures are partly governed by the principles of conditioned reflexes (Chapters 1 and 4) a fact that has profound implications for the theoretical aspects of the proposed model as for clinical methods used for treatment of the kinds of tinnitus that cause suffering. A conditioned reflex that can evoke a reaction is created when there is a temporal coincidence of a sensory stimulus and reinforcement

(reward or punishment). The causal relation between stimulus and reinforcement is not necessary to create a reflex but temporal coincidence is sufficient. For example, perception of tinnitus while a person is under strong negative emotions would be sufficient to initiate a conditioned reflex. At the initial stage of tinnitus development, cognitive processes may play a dominant role including the fear of not being able to improve tinnitus and the potential medical problems linked to it.

Once the reflex is established then the sensory stimulus without the need for reinforcement is sufficient to evoke a negative reaction. Clinically significant tinnitus (suffering) is typically continuous

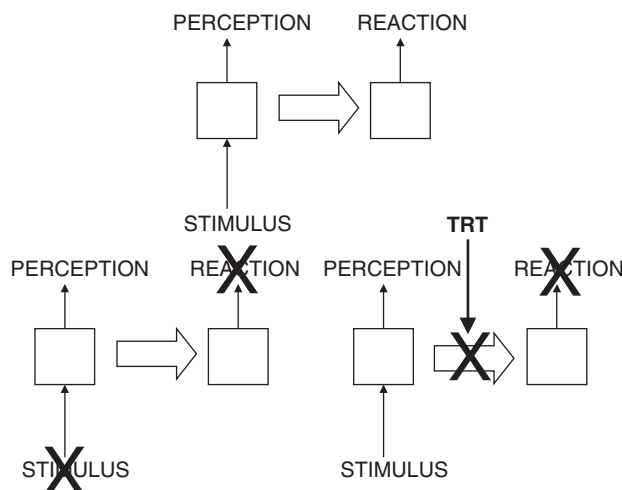


Fig. 2. The mechanisms of TRT action as compared with other approaches. Note, that TRT is neither aimed at modifying abnormal neural activity that causes the tinnitus nor at direct modification of tinnitus-evoked reactions but at blocking functional connections between sensory (auditory) and parts involved in generating reactions (the limbic and autonomic nervous systems).

and the reactions induced by the activation of the autonomic nervous system act as negative reinforcement. Tinnitus-related neuronal activity acts as a stimulus and the reaction evoked by activation of the sympathetic part of the autonomic nervous system act as reinforcement. Consequently, once the initial association between tinnitus perception and some negative event happening at the same time develops, the reflex loop is rapidly enhanced, as both stimulus and reinforcement are continuously present. Furthermore, the likelihood of spontaneous improvement of tinnitus, which would reflect the extinction of this reflex is low.

Most treatments proposed for tinnitus aim at reducing the tinnitus-related neuronal activity (e.g., by medications, electrical or magnetic stimulation and masking, see Chapters 34–39) or at decreasing tinnitus-induced reactions (e.g., psychological treatments aimed at improving coping, attention distraction, psychotropic medications acting at the limbic system). TRT differs from these approaches as it is aimed at changing specific functional connection between the auditory and the limbic and autonomic nervous systems without the attempt to change the abnormal neural activity that causes the tinnitus or directly attenuate tinnitus-evoked reactions (Fig. 2).

It has been recognized that processing of information at a subconscious level plays a significant role in learning, as well as in many other aspects of life. Reflex reactions and learning can occur without the conscious perception of a stimulus (Ohman, 1988; Esteves et al., 1994; Morris et al., 1998). Once the conscious and subconscious loops are created, the subconscious path could become dominant and therefore attenuating the conscious path alone might not be sufficient to alleviate the suffering from tinnitus. Results from Emory Tinnitus & Hyperacusis Center support this hypothesis by showing that a percentage of time during which the patients were aware of tinnitus and their subjective perception of its loudness did not have significant impact on the severity of the tinnitus as evaluated by the Tinnitus Handicap Inventory.

Physiological basis for TRT

The neurophysiological model of tinnitus described earlier (Jastreboff, 1990; Jastreboff and Hazell, 2004) has made it possible to develop a method of treatment for tinnitus. Currently, there is no reliable method for attenuating the tinnitus source and achieving a cure. It has been hypothesized that tinnitus as a problem arises because an

abnormal conditioned reflex arc is created. However, any kind of conditioned reflex can be reversed and retrained by proper techniques. The brain exhibits a high level of plasticity making it possible to habituate to any sensory signal, if this signal does not have negative implications (Chapter 2). Therefore, by interfering with the tinnitus-related neuronal activity that occurs above the tinnitus source, it should be possible to block the spreading tinnitus-related neuronal activity to the limbic and autonomic nervous systems (habituation of reactions) and prevent activation of high cortical areas where it would be perceived (habituation of perception) (Fig. 3).

Habituation is a normal and essential feature of the brain and occurs automatically in response to any neutral or low importance stimuli. Necessity of habituation results from the fact that we can perform only one task at a time that requires full attention. The problem is how to manage the enormous amounts of sensory input that is received all the time. The solution to this problem is to select important stimuli and block unimportant stimuli at the subconscious level so that it does not reach higher levels of the CNS and reaching our awareness inducing perception and inducing reactions, thus habituation occurs to unimportant stimuli. The important question is then what stimuli are regarded as unimportant.

TRT is aimed at inducing and facilitating habituation of tinnitus (both reactions induced

by tinnitus and its perception). The primary goal is to habituate reactions. Once this is achieved and abnormal neural activity that causes the tinnitus become more abnormal, the habituation of perception will follow automatically. Therefore, TRT utilizes the natural feature of the brain aiming at its utilization at abnormal neural activity that causes the tinnitus. There are two main components of TRT, both strictly based at the neurophysiological model of tinnitus: (1) counseling and (2) sound therapy. The goal of counseling is to reclassify tinnitus into category of neutral stimuli. As long as tinnitus is judged as important or potentially threatening, its habituation is difficult. The role of sound therapy is to decrease the strength of abnormal neural activity that causes the tinnitus in systematic manner over the period of the treatment. Sound therapy is used as well to treat hyperacusis, which accompanies tinnitus in ~30% of cases (Jastreboff and Jastreboff, 2002).

As the treatment is aimed to work above the source of tinnitus, the etiology of tinnitus is irrelevant and TRT can be successfully used for any type of tinnitus as well as for somatosounds (it should not be ignored that a somatosound may indicate severe but treatable disorders of the vascular system). The final clinical goal of TRT is to reach a stage when tinnitus does not interfere with the patient's life. Specifically, tinnitus, when present, should not cause annoyance and the patient's awareness of the tinnitus should be so low that it does not influence normal life. The results of treatment of 303 consecutive patients at Emory who had initial THI score at least 36 showed that significant improvement was achieved after 1 month of the treatment with THI score decreasing from 65 to 46, followed by further consistent improvement when followed up to 18 months hyperacusis was dramatically improved after 12 months, and in majority of cases a cure was noted. Both mean the change of THI score and the average change for all these patients reached level of statistical significance after 3 months. After 12 months, 82% of patients showed statistically a significant decrease of 20 points from the initial score.

Results of open studies reported from other centers also consistently showed significant improvement in over 80% of the patients who were treated

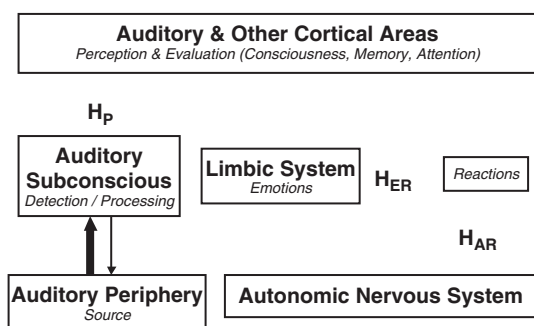


Fig. 3. Specific functional connections at which habituation of tinnitus occurs. H_p : habituation of tinnitus perception; H_{ER} : habituation of emotional reactions; H_{AR} : habituation of reactions evoked by the autonomic nervous system; H_p : habituation of tinnitus perception. Primary goal of TRT is to achieve habituation of reactions and then habituation of perception will follow automatically.

by TRT (Bartnik et al., 1999; Heitzmann et al., 1999; McKinney et al., 1999; Sheldrake et al., 1999; Herraiz et al., 2005; Mazurek et al., 2006a). The results of 5 years of follow up showed that the improvement is long lasting (Lux-Wellenhof and Hellweg, 2002). A systematic randomized study showed TRT to be highly effective, with highly statistically significant decline of THI and of percentage of time when tinnitus was annoying. Specifically, over period of 18 months in group with severe tinnitus THI decreased from 72 to 26.4; in group with mild tinnitus TRI decreased from 30.2 to 18.8. The percentage of time when patients were annoyed by tinnitus decreased from 47.3% to 6.3%. (Henry et al., 2006).

Conclusion

Tinnitus remains a challenging subject to study and to treat. The mechanisms are still poorly understood and there is no consensus regarding its optimal treatment. However, it appears that TRT provides an effective approach to alleviating the impact of tinnitus on patients' lives (the suffering) in a significant way. Additionally, TRT is also effective in treating hyperacusis. For TRT to be successful, it is important to follow the guidelines of the neurophysiological model of tinnitus for both counseling and sound therapy.

Abbreviations

CNS	central nervous system
DPOAE	distortion product otoacoustic emission
HL	hearing level
IHC	inner hair cells
OHC	outer hair cells
THI	tinnitus handicap inventory
TRT	tinnitus retraining therapy

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CHAPTER 41

Tinnitus activities treatment

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Abstract: Tinnitus Activities Treatment includes counseling of the whole person, and considers individual differences and needs. We consider four areas: thoughts and emotions, hearing and communication, sleep, and concentration. We typically use Partial Masking Sound Therapy, with a noise or music set to the lowest level that provides relief. A picture-based approach facilitates engagement of the patient, and provides thorough and structured counseling. We engage the patient by including homework and activities to demonstrate understanding and facilitate progress.

Keywords: tinnitus; tinnitus activities treatment; counseling; sound therapy; picture-based; partial masking

Background

Our counseling and sound therapy program began in the early 1980s by combining our “information counseling,” coping strategies and total and partial masking (e.g., Tyler and Baker, 1983; Tyler and Babin, 1986; Tyler et al., 1989; Stouffer et al., 1991). We suggested that it was important to consider “all the patient’s difficulties, not only an isolated problem” (Tyler and Babin, 1986, p. 3215). We recommend the use of our tinnitus problems questionnaire (Tyler and Baker, 1983) as part of our counseling to determine the difficulties that were especially important to the patient (“Please make a list of your difficulties which you have as a result of your tinnitus”).

Our work has been influenced by the Tinnitus Habituation Therapy of Richard Hallam and colleagues (e.g., Hallam et al., 1984, 1988, 1989; Coles, 1987; Coles and Hallam, 1987). Peter Wilson and colleagues (Wilson et al., 1993;

Wilson et al., 1998; Henry and Wilson, 2001, 2002) provided clear examples of patient activities.

Our sound therapy is mainly focused on Tinnitus Partial Masking, “so that both the tinnitus and noise are heard” (Tyler and Babin, 1986, p. 3213; Bentler and Tyler, 1987; Tyler and Bentler, 1987). We “urge the patient to use the lowest level masker that provides adequate relief” (Tyler and Babin, 1986, p. 3213). Sound therapy is not used in all patients, and we do not insist that the noise be present all the time. Hearing-impaired people often experience difficulty hearing noise (e.g., Tyler et al., 1983), and in some situations they prefer to hear better than obtain the partial relief of tinnitus provided by noise. We also use soft background music in place of background noise with some patients.

Activities therapy

Clinical experience treating tinnitus patients and discussions with other colleagues resulted in the classification of different groups of problems faced

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by tinnitus patients. These problems can be divided into four broad categories:

- Thoughts and emotions
- Sleep
- Hearing and communication
- Concentration

Patients who suffer from impairments in these categories may find that the impairments create additional personal and social problems. An all-encompassing treatment plan should address each of these categories. However, if a patient is not troubled by all of the areas, the clinician can choose to abbreviate or omit a particular section from the counseling. That being said, it may still be important to cover all the categories — as an area that is not problematic for the patient at that particular time may become problematic later on in life. The counseling that is provided in each of these areas will be described in more detail throughout this chapter. In addition, all of the counseling materials can be found via the World Wide Web through the University of Iowa Hospitals & Clinics, Department of Otolaryngology, Tinnitus Clinic website or at: <http://www.uihealthcare.com/depts/med/otolaryngology/clinics/tinnitus/activitytherapy.html>.

Typically, the counseling information is spread out over several sessions. In that manner, patients are able to practice the activities outside the clinic and upon further sessions provide feedback in regards to their progress. In addition, as the information is spread out over several sessions, key concepts are reiterated and patients are not overloaded with too much information at one time.

Selection of which of the four activities to administer

Since not every patient will require treatment in each of the four activities, the clinician needs to determine which areas require treatment. To assist in this, the Tinnitus Activities Questionnaire is administered (see Appendix). This questionnaire produces a score in each of the four areas (thoughts and emotions, sleep, hearing and communication, and concentration) and, in conjunction with

discussing these four areas with the patient, an overall treatment plan can be devised.

Thoughts and emotions

Patients with problematic tinnitus often are experiencing problems in many other aspects of their life that are unrelated to tinnitus. The clinician first needs to determine what the patient's major concerns are with regard to their tinnitus. In some cases, patients suffer from problems that are beyond the clinician's expertise and, therefore, appropriate referrals need to be made to a clinical psychologist or psychiatrist.

The thoughts and emotions section can be broken down into four categories:

- Listening to the patient
- Providing information about hearing, hearing loss, tinnitus, and attention
- Ways to make tinnitus less important
- Changing the reaction to tinnitus

Listening to the patient

The first step the clinician needs to take is to evaluate what is most important for the individual patient. What brought him to seek information? What are her/his expectations? Does he or she have a support system in place? Are there other stressors in the patient's life in addition to tinnitus? Asking specific questions can help obtain these answers and can influence the direction of counseling. Having the patient describe how tinnitus has affected their life can also be a useful way to begin. It may be beneficial to let the patient openly discuss their fears and concerns as this may serve as a therapeutic tool. In many cases, the patients have not had the opportunity for someone to listen to their concerns.

Providing information about hearing, hearing loss, tinnitus, and attention

Providing basic information to patients can be helpful for several reasons. The basic information

given to patients helps them realize they are not alone in having tinnitus. In addition, a general understanding of hearing, hearing loss, and tinnitus removes misconceptions and some of the fear patients may have of the unknown. It also assists patients in being able to develop realistic expectations with regard to what can and cannot be changed.

Patients are shown pictures to better understand the concept of how the nerves and brain code information. This neural activity is used to code the presence of acoustic sound. However, patients are informed that even without sound, there is random spontaneous activity in the nerves and in the brain. Later in the therapy session, the clinician discusses how tinnitus is likely coded in spontaneous activity. See Fig. 1 for a picture describing spontaneous activity that is shown to patients.

Many patients have similar thoughts about their tinnitus and the following questions are addressed:

- “Am I going to become deaf?”
- “Do I have a tumor?”
- “Will my tinnitus get better or will it get worse?”

Activities Therapy follows the work of Hallam (1989), who emphasized the importance of hearing and attention. For example, he noted that individuals normally attend to only one thing at a

time. However, our attention can be diverted to things that are unusual or surprising. (Figure 2 illustrates things that can influence our attention.) Hallam (1989) gave the example of a refrigerator hum being repetitive and meaningless so our brain automatically tunes it out over time. Tinnitus can be comparable to this in that it is also repetitive and not unusual. If an individual decides tinnitus is important for the brain to monitor, then he or she will not be able to habituate to tinnitus and the tinnitus will continue to be consciously attended to. However, if the patient with tinnitus decides the tinnitus is not important, it will be easier to ignore it and focus his or her attention elsewhere. Hallam suggested that most people can learn to not attend to tinnitus in ~18 months.

Ways to make tinnitus less important

Activities Therapy is designed to help patients change the way they think about and react to their tinnitus. Many patients come to the clinic with very negative views about their tinnitus. It is important for the clinician to understand how the patients view their tinnitus and why it is that they view it in that manner. As one way of making tinnitus less important, patients are encouraged to refocus their attention on other activities, such as joining new clubs and learning new tasks. Activities Therapy strongly promotes this and goes as far as challenging patients to seek out new

Tinnitus is likely the result of an increase in spontaneous nerve activity

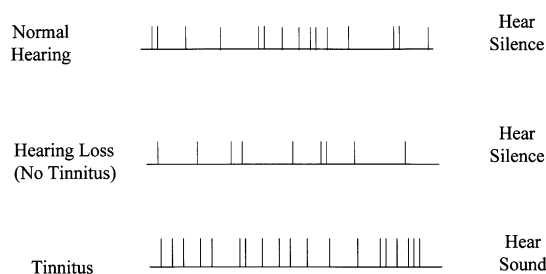


Fig. 1. Picture used to illustrate spontaneous neural activity.

Several things can influence our attention

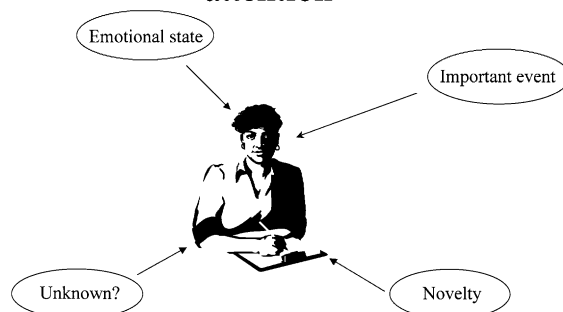


Fig. 2. Picture showing factors that affect our attention.

activities to pursue or to consider starting an activity or hobby they have always wanted to try. However, patients should not try to stay busy merely to escape their tinnitus. It is important for hobbies and activities to hold some intrinsic value for patients in order to make them meaningful. It is equally important for patients to understand that many people have tinnitus and are able to lead a happy and productive life. In that manner, group counseling (Newman and Sandridge, 2006) can sometimes be an effective way for patients to learn this from one another.

Changing the reaction to tinnitus

It is also important for the clinician to discuss and address how tinnitus is affecting a patient, typically in the areas of sleep, hearing, and concentration. By addressing the patient's most problematic situations, this can help improve the patient's emotional well-being. One way to address the most problematic situations is to have patients use a "tinnitus diary" for the first few weeks of treatment. They are asked to describe situations where their tinnitus is better and situations where their tinnitus is worse (Stouffer and Tyler, 1990). By having this specific assignment to work on, patients typically find that there are many situations in their life that tinnitus does not affect. In the tinnitus diary, patients are also encouraged to create a list of alternative activities to engage in when tinnitus is bothersome. Activities Therapy only recommends this diary for a few weeks, as the goal is to help the patient move away from thinking about their tinnitus.

The use of background sound and partial masking to manage tinnitus has been beneficial for many patients. A wearable device that produces sound is helpful for some patients, but is not for everyone. Clinicians discuss with patients some activities related to background sound and provide a rationale for adding this into their lifestyle. Having the understanding of how to implement background sound is helpful for all four areas and is relatively easy to implement into one's lifestyle.

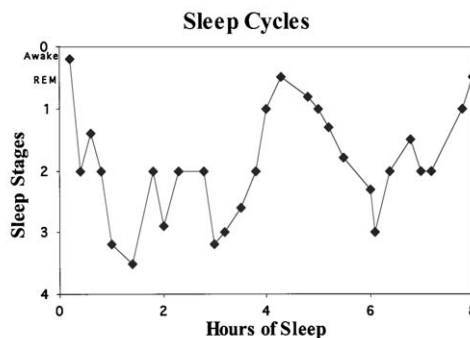
Sleep

Sleep disturbances are very common in tinnitus patients (e.g., Tyler and Baker, 1983; [McKenna, 2000; McKenna and Daniel, 2006]). Some patients report difficulty falling asleep, waking during the night, early awakening, or being tired during the day. Being under emotional stress combined with having difficulty concentrating and hearing can also contribute to fatigue. Activities Therapy regarding sleep includes:

- Understanding normal sleep patterns
- Factors that can affect sleep
- Arranging the bedroom
- Daytime and evening activities to promote sleep
- Using background sound to reduce the prominence of tinnitus
- The use of relaxation exercises

Understanding normal sleep patterns

Some patients will have misconceptions about what normal sleep patterns consist of. Therefore, information is provided to them in regard to the different sleep cycles and the amount of sleep required by most adults. (See Fig. 3 for an example of a picture used to illustrate the normal stages of sleep.) Many patients feel that their tinnitus is the reason they wake up during the night, but as



Normal stages of sleep during one night. Sleep stages cycle from light (stage 1) to deep (stage 4) and the cycle can repeat many times.

Fig. 3. Picture used to illustrate the normal stages of sleep.

McKenna and Daniel (2006, p. 88) point out, patients wake up through the “night at times predicted from a typical sleep cycle.” However, once awakened, the tinnitus can cause difficulty falling back asleep because the sound of the tinnitus is the first thing a patient may be aware of.

Factors that can affect sleep

There are many factors that can affect the amount and quality of sleep a person receives. The reasons can range from experiencing more stress in one’s life, to environmental factors such as light, noise, or temperature, to irregular work schedules. It is important to isolate these factors and, if applicable, recommend that the patient eliminate or modify one’s lifestyle to reduce these factors.

Arranging the bedroom

The arrangement of a patient’s bedroom can play a role in the quality of sleep. Having comfortable bedding and removing non-sleep related items such as the television, computer, food, and drink helps support the area for sleep. Making sure the bedroom is dark enough also promotes the bedroom for sleeping.

Daytime and evening activities to promote sleep

It is important to stress that patients who have difficulty with sleep should avoid napping during the day to “make up” for a poor night’s sleep. Getting regular exercise at least 3–4 h prior to bedtime may help those with sleep problems. It is important that the patients try to lead their life as normally as possible, even if they had a poor night of sleep. Those that have difficulty falling asleep on a regular basis should abstain from alcohol, caffeine, smoking, and eating large meals before bedtime.

Using background sound to reduce the prominence of tinnitus

There are several options for the use of background sound (quiet music, nature sounds) for

facilitating sleep. McKenna and Daniel (2006) recommend playing the background sound at all times in the bedroom. In this manner, patients make the background sound part of their environment and they do not have to consciously think about turning the sound on or off. Another option would be to start the background sound when the patient is trying to fall asleep and let the sound play the entire night. A third option is to use a timer, where the background sound shuts off after a specified period of time. Using background sound in the third option may be easier for significant others who will be sleeping in the same room. Some disadvantages of using the timer are that a patient may hear the sound turn off and if the patient wakes in the middle of the night and he or she wants to turn the sound back on, it may get him or her thinking about the tinnitus again.

The use of relaxation exercises

Patients who have tinnitus and difficulty with sleep may also benefit by using relaxation exercises. Progressive muscle relaxation and imagery training are two examples of relaxation training that patients can use to achieve mental calmness (Henry and Wilson, 2002). In using these exercises, a sense of relaxation can help improve the quality of sleep and may shorten the amount of time it takes to fall asleep. In addition to tinnitus, using relaxation exercises can carry over to other areas of a patient’s health.

Improving hearing and communication

Another goal of Activities Therapy is to help the patient understand what role tinnitus can have in affecting the patient’s hearing abilities. Therefore, the clinician discusses strategies for patients to use to improve their hearing. Improving hearing should:

- Alleviate some of the communication difficulties that can be associated with hearing loss.
- Improve communication difficulties associated with tinnitus.

- Reduce stress that can be associated with communication.

Hearing and hearing loss

First and foremost, it is the clinician's responsibility to ensure that the patient understands hearing and hearing loss. In addition, understanding what are the perceptual consequences of hearing loss and what sounds may no longer be audible to them is also important. If the patient is a hearing aid candidate, the benefits and limitations of amplification are discussed. Likewise, patients are informed of the availability and options they have for assistive listening devices. Equally important, the clinician leads a discussion on the importance of a good signal-to-noise ratio, ways to ensure this, and the effects it has on their hearing abilities.

Hearing difficulties due to hearing loss and tinnitus

Many patients who experience both tinnitus and hearing loss put the blame of their hearing difficulties on their tinnitus, even if they have a significant hearing loss. Therefore, it is essential to help patients understand what can be explained by the degree of hearing loss and what can be explained by their tinnitus. Especially important for a patient with a hearing loss to understand is that even if the tinnitus were taken away, the hearing loss would still be there. During this discussion, the clinician explains that tinnitus is not the cause of hearing loss, but it can produce hearing difficulty by distracting one from listening. The ringing, buzzing, or roaring sound of the tinnitus can also produce a masking of some sounds (Surr et al., 1985; Melin et al., 1987). In addition, the clinician explains to patients that hearing loss can cause difficulties in distinguishing one sound from another because the tinnitus sound can be confused with other sounds that have the same pitch as the tinnitus. The clinician also discusses factors that affect communication, such as the ability to see the talker, familiarity with the talker, familiarity with the topic of discussion, and the patient's stress level.

Strategies to improve hearing and reduce stress

There are three main areas that are discussed in detail to help patients better manage their hearing loss. The areas consist of amplification, the environment, and communication.

Amplification

The first step in managing a hearing loss is to make sure that patients are fit with an appropriate hearing device (Searchfield, 2006). Hearing devices may include hearing aids, assistive listening devices, and/or cochlear implants. Appropriateness of devices, functions of devices, benefits, and limitations are all addressed by the clinician. Also discussed with them are the advantages of binaural hearing aids (Brooks and Bulmer, 1981; Balfour and Hawkins, 1992). In addition, if the patient is already wearing a hearing device or owns a device that is in good working order, the clinician checks the appropriateness of the fit. Any remaining questions that the patient may have about their current devices are answered.

Environment

The environment is not always something patients consider when they think about their hearing abilities. Clinicians play a valuable role in teaching the patient what characteristics are most suitable for facilitating a conversation. The clinician teaches the patient that environments with the following characteristics are optimal (Dillon, 2001):

- Good lighting
 - Making sure that there is adequate light to illuminate the face of the communication partner without shadowing it.
 - Moving away from light that is shining directly in the listener's eyes and making it difficult to see the communication partner's face.
- Positioning
 - Being in close proximity to the communication partner, which enhances the signal-to-noise ratio.

- Making sure that the face of the communication partner is visible and not in profile.
- If there is an asymmetric hearing loss, have the patient position so that the ear with better hearing is closest to the talker.
- Minimizing visual distractions
 - Closing a door to eliminate movement from another room.
 - Closing a window to eliminate blowing curtains.
 - Turning off a television.
- Minimizing noise
 - Turning off extraneous machines (TV, radio, kitchen appliances, etc.).
 - Closing doors and windows to minimize background noise.

Communication

Another concept Activities Therapy emphasizes is to empower patients to take charge of their hearing loss by being an effective communication partner. Many patients may not know what this entails, so the definition of assertive communication is given and compared with passive and aggressive communication styles (Tye-Murray, 1998). Examples are given of the different types of communication styles and the patients are encouraged to discuss what type of communicator they think they are. To further explain this, a problematic situation can be demonstrated and the following points are discussed:

- Use of repair strategies to fix communication breakdowns (i.e., asking individuals to slow down, use clear speech, repeat, rephrase, reduce, and/or elaborate sentences).
- Use of anticipatory strategies prior to communication interactions (i.e., knowing the topic and/or key vocabulary words, using relaxation techniques, and/or practicing dialogue).
- How to disclose hearing loss to potential conversation partners, when appropriate.
- Speech-reading strategies (i.e., lip reading, facial gestures, and body movements).

Many patients that have tinnitus experience great difficulty in being able to concentrate on tasks. In Activities Therapy, three areas are addressed to improve concentration in patients with tinnitus: providing information, decreasing the prominence of the tinnitus, and increasing attention to the task at hand.

Provide information about concentration difficulties

In our world today, we have a lot of distractions in the visual and auditory domain. The environment plays a large role in how well one can concentrate. For example, there may be extraneous noises, distractions, poor lighting, and inconsistent temperature that may or may not be under our control. Also, distracting stimuli can be annoying, fearful, loud, unpredictable, and uncontrollable. One's own physical state can affect concentration as well, especially if the person is hungry, tired, or overall not feeling well. In addition, a patient's emotional condition can influence how well he or she can concentrate. For example, high levels of anxiety or a state of boredom can disrupt an individual's concentration ability.

With regard to concentration abilities, there is a large variance among individuals. For example, some people cannot read in a noisy coffee shop, whereas others can do so easily. Most individuals have the ability to focus their attention on a particular task for at least some period of time. An example of this is that some individuals with chronic pain can successfully train themselves to focus their attention away from their discomfort and onto other activities. Another example - is an athlete competing in a competitive basketball game and trying to ignore the hostile fans while shooting a free throw. Some people spend their energy concentrating on their tinnitus and therefore struggle focusing on a particular task.

However, not everyone is distracted by his or her tinnitus. Patients are encouraged to list situations when the tinnitus does not interfere with their concentration. The goal is to try to figure out what is different about these situations, and

whether or not the characteristics can be transposed to other situations.

Decreasing the intrusiveness of the distracter

The degree of the intrusiveness can depend on the task at hand. For some patients, simple tasks (e.g., filing) may not be stimulating enough and the tinnitus can fill in as the concentration demand is low. On the other hand, some patients find that when performing a complex task, (e.g., learning a new computer program) the tinnitus does not have the ability to interfere or intrude as the concentration demand is very high. This can vary from patient to patient. Therefore, patients are encouraged to consider task difficulty when dealing with tinnitus and to try both simple and complex tasks.

Many people find benefit from using sound therapy to reduce tinnitus' distracting nature. Partial masking is often recommended either with wearable or non-wearable devices. Music is also encouraged, and soft, pleasant music without a lot of beat changes (e.g., classical music) is usually recommended. Patients are educated that sound therapy can be incorporated into a lot of daily activities in a relatively easy fashion.

Facilitating focusing attention on the task

Henry and Wilson (2001, p. 78) describe an "Attention Control" approach to help tinnitus patients that refers to the "ability to switch attention from one stimulus to another by self-control." This is presented to patients and at first it may be easier for patients to begin practicing with physical sensations, such as the sensation of having clothing on the skin. Practice continues with external sounds and then moves to their tinnitus. Patients are taught that there are some aspects of their attention they can control, and that with practice it is possible to divert their attention away from their tinnitus and onto other tasks.

Equally important for good concentration are some strategies to stay focused on the particular

task. For example, actively participating, asking questions, and taking notes during an important meeting helps keep one's focus on the task at hand. If patients have complex tasks that require focused and prolonged concentration, these may be reduced to smaller tasks requiring less intense concentration. For tasks that require intense concentration, it is suggested to work on those tasks for shorter periods of time. Reading is one task that can easily be segmented into shorter intervals. In addition, if the patient is experiencing severe difficulties with concentrating on a task, the patient is encouraged to vary the amount of time spent on each task, or build up the time spent on each task and to eliminate any distractions that may be interfering with their concentration.

Self-confidence can also help a patient concentrate. Learning a new task can increase motivation. Finding success in an activity they have not been able to complete in awhile is a confidence booster. When patients are able to experience success with their concentration abilities, they may feel greater control over their concentration skills and be more confident when undertaking future tasks.

Conclusion

We have outlined our counseling and sound therapy approach to treat tinnitus patients (see also Tyler, 2006). The information is divided into four areas, depending on the needs of the patient: thoughts and emotions, sleep, hearing and communication, and concentration. This therapy was started in the 1980s with our Informational Counseling approach and since that time has been strengthened from the work of Hallam (1989) and Henry and Wilson (2001).

Acknowledgments

We wish to acknowledge the grant support provided by the American Tinnitus Association and the National Institutes of Health (NIH Grant 5R01DC005972).

Appendix: Iowa Tinnitus Activities Questionnaire

Name:

Date:

Please indicate your agreement with each statement on a scale from 0 (completely disagree) to 100 (completely agree).

No.	Statement	0–100
1	My tinnitus is annoying.	
2	My tinnitus masks some speech sounds.	
3	When there are lots of things happening at once, my tinnitus interferes with my ability to attend to the most important thing.	
4	My emotional peace is one of the worst effects of my tinnitus.	
5	I have difficulty getting to sleep at night because of my tinnitus.	
6	The effects of tinnitus on my hearing are worse than the effects of my hearing loss.	
7	I feel like my tinnitus makes it difficult for me to concentrate on some tasks.	
8	I am depressed because of my tinnitus.	
9	My tinnitus, not my hearing loss, interferes with my appreciation of music and songs.	
10	I am anxious because of my tinnitus.	
11	I have difficulty focusing my attention on some important tasks because of tinnitus.	
12	I just wish my tinnitus would go away. It is so frustrating.	
13	The difficulty I have sleeping is one of the worst effects of my tinnitus.	
14	In addition to my hearing loss, my tinnitus interferes with my understanding of speech.	
15	My inability to think about something undisturbed is one of the worst effects of my tinnitus.	
16	I am tired during the day because my tinnitus has disrupted my sleep.	
17	One of the worst things about my tinnitus is its effect on my speech understanding, over and above any effect of my hearing loss.	
18	I lie awake at night because of my tinnitus.	
19	I have trouble concentrating while I am reading something in a quiet room because of tinnitus.	
20	When I wake up in the night, my tinnitus makes it difficult to get back to sleep.	

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CHAPTER 42

Sound therapies for tinnitus management

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Abstract: Many people with bothersome (suffering) tinnitus notice that their tinnitus changes in different acoustical surroundings, it is more intrusive in silence and less profound in the sound enriched environments. This observation led to the development of treatment methods for tinnitus utilizing sound. Many of these methods are still under investigation in respect to their specific protocol and effectiveness and only some have been objectively evaluated in clinical trials. This chapter will review therapies for tinnitus using sound stimulation.

Keywords: sound therapies; tinnitus; hyperacusis; overview

Introduction

Tinnitus is not a physical sound; it is a phantom auditory perception (Jastreboff, 1990) and at the present time it cannot be measured objectively. Attempts to apply the rules of acoustics to tinnitus such as phase cancellation have failed resulting in unsuccessful trials to attenuate tinnitus (Jastreboff and Hazell, 2004). Similarly, the efforts to maximize the masking by using masking sounds that have a frequency that is similar to the pitch of the tinnitus have failed as an effective treatment of tinnitus (Penner, 1987; Jastreboff and Hazell, 2004).

Silence-induced tinnitus

Temporary tinnitus can be induced in almost everyone when a person is placed in a sufficiently quiet environment for some time (Heller and

Bergman, 1953; Tucker et al., 2005). The descriptions of this sensation varies (e.g., ringing, buzzing, hissing), but they are similar to those reported by individuals who have tinnitus when in a normal sound environment. Preliminary studies of psychoacoustical characterization of silence-induced tinnitus (pitch match, loudness match, minimal masking levels) have confirmed this observation (Walck et al., 2007). It may be hypothesized that a specific tinnitus signal exists in the neural networks of every person, but the strength of this signal is normally very low and it is not perceived as a sound in the presence of normal natural sounds from the environment. When the background sound is low then tinnitus may emerge. Two mechanisms may be involved in this process. First, the gain within the auditory pathways increases when sounds that reach the ear have a low level and the sensitivity of neurons in the auditory pathways increases (Gerken, 1992, 1993; Boettcher and Salvi, 1993; Salvi et al., 1996). Second, all senses (including hearing) do not react to the absolute value of a stimulus, but to the difference between a stimulus and the background. The

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strength of any signal within the nervous system is related to its contrast with regard to the background neural activity. If for some time a person is in a silent environment, weak sounds (e.g., heart beat) become noticeable and appear to be louder than they appear in the normal background of sounds.

The same applies to internal signal of tinnitus and indeed individuals with tinnitus report that their tinnitus seems to be louder and more intrusive when they are in a quiet surrounding or when their ears are blocked.

On the other hand, it is also a common observation that individuals with tinnitus are less annoyed by tinnitus when in a sound-rich environment. The gain within the auditory system decreases as a result of systematic exposure to enriched sound background (Formby et al., 2003). Additionally, by increasing background neural activity, it is possible to decrease effectively the strength of tinnitus-related neural activity within the auditory pathways and consequently in all systems in the brain involved in shifting tinnitus from just an experience into tinnitus, which is a disturbing problem.

Effect of tinnitus on non-auditory systems of the brain

Decrease in the strength of the tinnitus signal within the auditory pathways has further positive consequences. Tinnitus that is bothersome activates other systems in the brain than tinnitus that is not bothersome. All system in the brain act in a dynamic balance scenario; therefore, the decrease of the strength of tinnitus-related neural activity in the auditory system results in lowering of the activation of the limbic and autonomic nervous systems, which have been identified as involved in clinically significant tinnitus. Tinnitus is then less intrusive, causes less annoyance, and the activation of the systems, which are outside of our conscious control are decreased and negative effects on the individual's life diminish and tinnitus ceases to be a problem.

Our everyday environment contains a variety of sounds, softer and louder, predictable and unpredictable, pleasant and unpleasant. Most of them

are in the background and unnoticed (i.e., they undergo spontaneous habituation). Particularly many sounds of nature, such as rain or wind are easy to habituate. We are used to the presence of these sounds and they do not induce negative reactions. Everyday neutral sounds, such as a fan, heating or air conditioning systems are known to be easily acceptable as well. The sounds of water, such as a brook or rain, delivered by table-top instruments can be used for a long time without inducing annoyance.

All these sounds can enrich sound backgrounds. Music plays a special role when used to enrich background and music is known to reduce stress, promote learning, help to induce changes in cognitive functions, and promote recovery from traumatic events including health problems (Lipe, 2002; Nickel et al., 2005). Many tinnitus sufferers have noticed that their tinnitus is less intrusive when they are listening to music or relaxing sounds that they like. This means that an enriched sound environment can reduce the gain within the auditory pathways and interferes with detection and processing of tinnitus, leading to a weakening of the perceived tinnitus.

Consequently, recommendations to “avoid silence” and enrich the background sounds should be the first advice to people who have problem with tinnitus, disregarding specifics of other treatments used.

The positive effect of background sound became a starting point to many sound therapies utilized in treatment of tinnitus. Specific goals of these therapies vary, and may focus on covering up tinnitus (masking), distraction attention, lowering stress level, or decreasing the strength of tinnitus signal. Artificial sounds that have been utilized include white noise (equal energy across the frequency range), pink noise¹ into the protocol.

Sound as a treatment for tinnitus

There are many methods by which the sound can be delivered. It can be background sound present

¹Pink noise, also known as 1/f noise, is noise the energy of which fall 3 dB/octave.

in the environment, or produced by table-top sound machines, played by CD, tape, mp3 players, radio, or by specific ear level devices, sound generators, producing broad band noise. Patients can be exposed to sound in an open field or use earphones and sound can be amplified by hearing aids. More defined types of sounds are used in many forms of sound therapies such as pink noise therapies, Dynamic Tinnitus Mitigation System, Phase Shift Tinnitus Reduction, Auditory Integration Training, masking/relief therapy, music therapies, Neuromonics Tinnitus Treatment, and Tinnitus Retraining Therapy (TRT) (Vernon and Meikle, 2000; Jastreboff and Hazell, 2004; Nickell et al., 2005; Argstatter et al., 2006; Henry et al., 2006; Herraiz et al., 2006; Davis et al., 2007). They widely vary in their recommendations as to when and how sound should be delivered. For example, patients might be advised to use sound only when tinnitus is annoying, a few times a day, as an exercise in set times, when convenient, or all the time. The counseling related to the use of such sound varies from none to very extensive ones covering many aspects of the auditory system and brain function (see Chapter 40). Many of these therapies were never evaluated and their efficacy has mostly been supported by anecdotal reports or by testimonials of individual patients.

Different sounds used in treatment of tinnitus

The set of CDs, known as Dynamic Tinnitus Mitigation System, is aimed at tinnitus masking and offers different sounds, such as the sound of water, nature, or air. These artificial sounds are prepared to enhance masking properties. The system might be helpful for patients whose goal is suppressing their tinnitus as it offers sounds more acceptable than white noise. Indeed, the best acceptable sounds from these systems are sounds that closely resemble the sounds of nature (Henry et al., 2004). The effectiveness of these systems have not been proven.

What is known as pink noise¹ therapies do not utilize a true pink noise, but rather an acoustic signal with various spectral properties. The sound used varies in intensity and the exposure to the

sound is for a limited time during the day (Vernon and Press, 1998; Vernon and Meikle, 2000). Its effectiveness has not been proven.

Phase Shift Tinnitus Reduction Therapy is a recent attempt to eliminate tinnitus by using phase cancellation technique. In case of external sound, it is possible to achieve the cancellation of sound by creating its reversed version (phase shift of 180°) and mixing it with the original sound. This technique is successfully utilized in Active Noise Cancellation headphones for real sounds. Past attempts to cancel tinnitus were not successful. Since there is no physical vibratory activity on the basilar membrane of the cochlea corresponding to tinnitus perception, tinnitus cannot be canceled. In Phase Shift Tinnitus Reduction Therapy tinnitus is matched and then reproduced while changing the phase difference between the sounds applied to the two ears mimicking tinnitus, cyclically through all possible values in 10° steps from 0° to 360° (“Method and apparatus for treatment of mono-frequency tinnitus” United States Patent 6846284). This approach might have an effect on tinnitus due to potential different effects of external sound on tinnitus dependent on its phase shift between ears. Proponents of this technique claim that 83% of patients have a positive response in the case of tonal tinnitus, but these results were not confirmed in the independent studies.

Auditory Integration Training originally developed by Alfred Tomatis and utilized for autistic children (Mudford et al., 2000; Thompson and Andrews, 2000) was first implemented for tinnitus by G. Berard (Tharpe et al., 2004). The treatment involves listening during two 30-min sessions per day for 10 days to a specifically pre-processed music, altered in such a way that high frequencies and low frequencies are randomly shifted. This procedure results in the perception of distorted sound. Its effectiveness for tinnitus has not been proven.

Music therapy has been utilized in Europe for many years for a variety of problems. Different types of music, frequently tailored to specific patients, are used typically in combination with other therapies aimed at decreasing the stress levels. The Heidelberg music therapy protocol for chronic tinnitus is probably one of the most

structured and evaluated treatments. This approach should be helpful for some tinnitus patients, however, there are only limited data indicating its effectiveness (Argstatter et al., 2006).

Masking

Recently masking therapy is promoted as relief therapy, where the use of any sound is acceptable as long as it provides some immediate relief. A systematic clinical study comparing this new version of masking therapy with TRT showed that, while TRT produced better results, nevertheless relief therapy can be effective for some patients, particularly those with low tinnitus severity (Henry et al., 2006).

Masking therapy is a method propagated by Vernon since the 1970s (Vernon and Schleuning, 1978; Schleuning et al., 1980). Its initial aim was to cover tinnitus perception through the use of external sound. While applying masking residual inhibition was sometimes observed as well, but it lasted only for a short time and thus did not offer a significant clinical benefit (Terry et al., 1983). The effectiveness of masking was restricted to a small group of tinnitus patients as shown over the years by a variety of studies (Hazell et al., 1985; Terry and Jones, 1986; Erlandsson et al., 1987; Penner and Bilger, 1989). Notably, masking of tinnitus prevents its habituation and patients who benefit from masking therapy need to continue using it for years (Jastreboff and Hazell, 2004).

Desensitization

For a long time, the term desensitization was used in a non-specific manner and reflected the process of decreasing the sensitivity of the auditory pathways to sound predominantly in patients with decreased sound tolerance was the problem. Commonly the procedure involved exposure to sound, typically starting from a low level and gradually increasing it. There was no standard protocol that has been published, except when it was a part of TRT, to treat patients with hyperacusis or patients

with both tinnitus and hyperacusis. Recently, the Neuromonics Tinnitus Treatment formerly known as an Acoustic Desensitization Protocol (Davis, 2006) was proposed as a means to help patients with tinnitus (Davis et al., 2007). It utilizes sound starting with higher levels of external sound and decreases it in stages over a period of approximately 6 months. The sound used consists of mixed pre-processed music and noise according to the proprietary algorithm and patients are expected to listen to it for 2h per day (Davis et al., 2007). The sound spectrum is shaped according to patient's audiogram to compensate for potential threshold shift up to 12.5 kHz. Initially the treatment is aimed at masking the tinnitus part of the time and later on it utilizes lower sound levels to maintain the effect. The treatment lasts for 4–6 months and includes counseling based on a wide variety of other techniques used to help individuals with tinnitus. Recently published data indicate that this approach can be effective for tinnitus (Davis et al., 2007).

Tinnitus retraining therapy

TRT (see Chapter 40) involves counseling and sound therapy, both strictly based on the neurophysiological model of tinnitus. The role of sound therapy in TRT is to decrease the contrasts between the tinnitus and background neural activity, to reduce abnormal gain in the auditory pathway, and to interfere with the brain's ability to detect and process the tinnitus signal. It always utilizes an enriched sound background — typically by tabletop sound machines producing sound of nature. While it is not necessary, in a majority of cases, ear-level instrumentation is recommended as well — sound generators for patients with relatively normal hearing and combination instruments or hearing aids for patients with tinnitus and hearing loss. It is the sound that is important, not any specific sound device. There is no need to tune the spectrum of the sound to the sound of tinnitus, but the spectrum of sound should cover a range of frequencies.

Detailed recommendations governing sound therapy in TRT were described in details

elsewhere (Jastreboff and Hazell, 2004) (see Chapter 40) and only the main rules are listed here.

The sound should never induce annoyance or evoke discomfort of any kind. It should not suppress (mask) tinnitus and it should be used 24 h a day. If the sound generators or combination instruments are used, the sound should be set at a level or just below “mixing point,” which represents the beginning of partial suppression of tinnitus, providing that this level of sound is still comfortable. Sound levels close to the threshold of hearing should be avoided. There is no necessity to use specific sound levels as long as these requirements are fulfilled. TRT seems to be effective for all types and levels of tinnitus (Jastreboff et al., 1996, 2001; Bartnik et al., 1999; Heitzmann et al., 1999; McKinney et al., 1999; Sheldrake et al., 1999; Herraiz et al., 2005; Mazurek et al., 2006).

Conclusion

In conclusion, sound therapies can offer significant benefit in treatment of tinnitus. It appears, that for low severity tinnitus different versions of sound therapy might be effective. As long as patients use sound and have received basic counseling, positive results are observed. For higher level of tinnitus severity, it seems to be important to implement sound therapy tailored to patient’s specific needs, combined with more extensive counseling. It is not clear which type of sound processing and protocol of sound use are optimal, but any sound is better than silence, as long as it is not annoying, creates discomfort, or damages hearing. There is no one generally accepted version of sound therapy and systematic studies are needed to identify the crucial factors.

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CHAPTER 43

Object identification and attention training for treating tinnitus

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Abstract: We hypothesize that abnormal attention and auditory scene analysis contribute to the severity of tinnitus and that the incongruence between tinnitus and normal auditory perception is responsible for its resistance to traditional sound-based habituation therapies. New methods of treatment using auditory and visual attention training are proposed as a means to augment counseling and sound therapies for tinnitus management. Attention training has been demonstrated to improve an individuals' ability to attend to relevant sounds while ignoring distracters. The main aim of the current study was to determine the effectiveness of structured Auditory Object Identification and Localization (AOIL) tasks to train persons to ignore their tinnitus. The study looked at the effects of a 15-day (30 min/day) take-home auditory training program on individuals with severe tinnitus. Pitch-matched tinnitus loudness levels (TLLs), tinnitus minimum masking levels (MMLs) and measures of attention were compared before and after the auditory training. The results of this study suggest that short-duration auditory training which actively engages attention, object identification and which requires a response from participants, reduces tinnitus. There was a greater effect on pitch-matched tinnitus MMLs than on actual TLLs. The reason(s) for this are unclear, although a correlation found between changes in MMLs and improvements in the ability to shift attention may be one underlying reason. Although this study followed a small number of participants over a limited time-span, it is believed that the training and accompanying model are a promising approach to investigate and treat some forms of tinnitus.

Keywords: auditory scene analysis; attention; training; treatment; tinnitus

Introduction

The last two decades have seen major advances in understanding the neurophysiology of tinnitus (Eggermont and Roberts, 2004) (see Chapter 2) and its similarities to chronic pain (Møller, 2000). An area which has developed slower is our understanding of the cognitive aspects of tinnitus

perception (Zenner and Zalaman, 2004). Simple perceptual constructs of tinnitus such as pitch and loudness may be insufficient as means of characterizing tinnitus. We need to extend our view of tinnitus as a phantom perception of a simple sound to incorporate concepts with greater ecological validity such as auditory object perception and figure ground differentiation (Winkler et al., 2006). The authors of this chapter consider that tinnitus is complex auditory activity that disobeys rules that normally apply to auditory object

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identification. We believe that abnormal attention (Hallam et al., 2004) and auditory scene analysis (ASA) (Bregman, 1990) contribute to the severity of tinnitus, and the incongruence between tinnitus and normal auditory perception is responsible for its resistance to traditional sound-based habituation therapies. The authors also acknowledge the importance of individual's reaction to tinnitus and non-auditory psychology (Henry and Wilson, 2001); but our research concentrates on how the perception of tinnitus and subsequent attention processes differ — or do not — from normal sound perception — and how a dichotomy of sound and tinnitus processing may account for over-attention to tinnitus. We believe that departures from normal auditory cognition lead to tinnitus' resistance to habituation. The model we present in this chapter suggests that auditory training should lead to a diminution of tinnitus annoyance by improving processing of normal auditory activity compared to tinnitus activity.

Most bothersome chronic tinnitus appears to be the consequence of the central nervous system's (CNS) plasticity that may become expressed in response to altered activity from the inner ear (see Chapter 2). Normally, we are not aware of the background activity (spontaneous discharge) occurring in the auditory nerve (Eggermont and Singer, 1995). However in a damaged inner ear, the rate and pattern of spontaneous discharge of the auditory nerve is altered (Martin et al., 1996; Searchfield et al., 2004). Increasing evidence from electrophysiology and imaging studies of the brain indicate that changes in output from the cochlea are enhanced by processing within the auditory pathways (Eggermont and Roberts, 2004). Changes in synaptic activity can lead to long-term anatomical and molecular change (Salvi et al., 2000). A persistent altered input to the central auditory system may result in functional changes in the auditory cortex similar to that believed to account for phantom limb pain in the somatosensory system (Muhlcnickel et al., 1998; Møller, 2006). There is evidence that some forms of tinnitus involves other parts of the CNS than those normally activated by sound (Møller et al., 1992; Cacace, 2003). There is significant evidence that various cross-modal pathways are involved in tinnitus

generation (Møller et al., 1992; Cacace, 2003). Some examples include: the modulation of tinnitus with oral-facial movements, with cranio-cervical manipulations, with finger and muscle movements (Levine, 1999) and skin stimulation and via trigeminal nerve interactions (Morgan, 1992). Normally the hearing system adapts to unimportant, continuous sounds. For a yet to be identified reason, the auditory system in many people with tinnitus does not habituate to the perception of tinnitus; instead it persists taking on an unusual importance (Cuny et al., 2004).

Perception is a mental representation of the world produced from the multitude of information impinging on our senses. In most environments a complex mixture of sounds reach the human ear. The auditory system needs to accurately separate out this input in order to make sense of the acoustic environment and 'pick out' relevant sounds. It is attention that allows us to select particular elements of sensory input for more detailed cognition (Spieth et al., 1954). A widespread, multimodal (auditory, visual, and tactile), cortical and sub-cortical network for the shifting of attention to relevant features of the sensory environment has been suggested on the basis of the results from neuroanatomical (Mesulam, 1981) and functional magnetic-resonance imaging studies (Downar et al., 2000). The ability to detect and then react to changes in the sensory environment is important for survival; thus, changes in the sensory environment are likely to draw attention involuntarily (Downar et al., 2000). For normal perception we must be able to select from the vast wealth of information entering the various sensory systems (Escera et al., 2000).

Attention is characterized by two aspects: selectivity and capacity limitation. Conscious perception is always selective. At any given moment we are aware of only a small fraction of the inputs stimulating our senses, as the brain continuously assigns priority to some sensory information over others (Pashler, 1998). While all conscious perception is selective to a certain degree, selective auditory attention refers specifically to the ability to select relevant information from surrounding sounds and ignore distracter stimuli (Giard et al., 2000) preferentially processing a particular set of

sounds at expense of others (Alain and Arnott, 2000). This selectivity is essential for efficient management of information relay to the brain (Hughes and Jones, 2003). While the allocation of attention is usually voluntary and selective, sometimes attention is directed involuntarily, resulting in distraction (Jones, 1999). Directed selective attention is therefore in a state of tension with automatic processing of unattended information. It is important to maintain the integrity of selective attention in regards to relevant information, but it is also necessary for irrelevant information to compete for and possibly win control of attention. In that case, irrelevant information cannot be completely neglected. A balance between engaging selective attention and allowing flexibility must be maintained, in order to adapt to the changing environment. Competition from irrelevant sounds is an essential element of perception — but irrelevant sounds can corrupt the integrity of processing attended sounds (Hughes and Jones, 2003).

In principle, information gaining access to a limited-capacity attention system is controlled by two types of processes: active selection (focused attention) and the breakthrough of unattended stimuli (passive attention). For optimal functioning in a real-world environment, a balance between top-down (active) and bottom-up (passive) attention mechanisms must be maintained. If, for example, top-down mechanisms dominate attention, relevant (potentially dangerous) events outside the focus of attention may be ignored. On the other hand, if bottom-up mechanisms capture attention too easily, increased distractibility may result, making goal-directed behavior impossible. Such top-down/bottom-up imbalances can be seen in individuals with attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder, dementia, schizophrenia, and brain injuries (Escera et al., 2000). Such an imbalance may also be found in conditions of milder injury or damage; for example, in tinnitus.

It is generally accepted that tinnitus does not obey many of the normal perceptual rules applying to sound (Henry and Meikle, 2000; Tyler, 2000). For example, tinnitus intensity matches are out of step with its perceived loudness — tinnitus may match to a quiet external sound but be perceived

by the sufferer as being as loud as a jet engine. Although tinnitus may have a low-intensity match it can be difficult to mask (cover) it, even with very loud sounds close to the presumed tinnitus pitch (TP) (Feldmann, 1971; Mitchell, 1983; Burns, 1984). The reason, we believe, lies in ASA (Bregman, 1990). In everyday life we often listen to one sound, such as someone's voice in a background of competing sounds. To do this we must assign simultaneously occurring sound features (frequency, intensity, timbre) to the correct source and organize sounds appropriately over time. Recent research has focused on the underlying neural basis of a form of sequential organization known as auditory streaming (Carlyon, 2004). Auditory streams are the “objects” of audition and may underlie ASA. Like objects of visual perception, auditory objects generally correspond to physical objects in the environment. Importantly, these objects can be selectively attended to, processed and followed over time; suggesting that auditory streaming processes either receives input from non-auditory areas or feed into processes that do. We hypothesize that neural activity forming tinnitus is sufficiently different from normal sound activity that when formed into a whole it conflicts with memory of true sounds (e.g., tinnitus does not localize to an external source. An inability to localize a sound source is “unnatural” and a violation of a fundamental perceptual process). We also believe that it is the lack of a context, or a lack of behaviorally relevant meaning, that forces the brain to repeatedly or strongly attend to the tinnitus signal. In the case of a refrigerator motor making a humming sound in the background, which is easily habituated to, the distal source of the noise can be paired with a visual or tactile perception as well; the context of the noise is not in doubt, nor is its meaning; it can be processed and dismissed as unworthy of further attention. There is no such context or intrinsic meaning for the tinnitus signal, which is endogenous and does not correspond to an auditory object.

An auditory object is the percept of a group of sounds as a coherent whole. Ideally, this unit represents a single acoustic source (Griffiths and Warren, 2004). Identification of an auditory object involves information being generalized between

particular sensory experiences in any one sensory domain (so that, e.g., we can recognize someone's voice over the telephone despite bandwidth distortions and understand a sentence regardless of accent or gender of the speaker; or we recognize the same face regardless of angle or lighting conditions). Auditory object identification is likely to involve at least two types of perceptual grouping — primitive grouping and schema-driven grouping (Bregman, 1990; Carlyon et al., 2001; Bey and McAdams, 2002; Alain and Izenberg, 2003; Sussman, 2005).

Primitive grouping is probably innate and pre-attentive and appears to follow the Gestalt principles of perceptual organization (Beauvois and Meddis, 1996; Moore and Egeth, 1997). The Gestalt psychologists of the early 1900s proposed a set of rules governing the formation of mental patterns from input sensory elements. These rules form the core of auditory grouping principles, which should also apply to tinnitus-related sensation.

As well as bottom-up primitive grouping, we also become aware of auditory objects by top-down processing. Schema-driven grouping relies on prior knowledge of familiar patterns in acoustic data. It involves past experience and context to organize sound into streams (Treisman and Gelade, 1980). Streams are then subjected to higher level processing. This in turn makes use of prior knowledge encoded in memory and “expectations” of what is likely and not likely (Cooke and Ellis, 2001). This model assumes that different qualities of the stimulus are not initially processed by the brain as a unit. Instead, different aspects, such as; what it is, where it is coming from, and who or what is producing it, are processed separately *and* simultaneously, before the stimulus is consciously perceived as a whole. This involves auditory stream segregation wherein sounds may be grouped to form meaningful representations of auditory objects in space. Features thought to play a key role in this auditory grouping include: spectral separation, spectral profile, harmonicity, onsets and offsets, coherent amplitude and frequency variations, spatial separation, temporal separation, bandwidth and phase (Moore and Gockel, 2002; Buchler et al., 2005). An auditory perception

which exists in the absence of some features should lead to abnormal perception (e.g., tinnitus).

Once the aberrant neural activity that causes the sensation of tinnitus is processed and fails to be matched to existing templates, further attention resources may be allocated to identify signal features (Fig. 1). Due to our limited attention capacity, attention will normally be allocated to one auditory object (or a small group of them) at a time. This is known as the figure, while all other auditory information is relegated to ground and remains undifferentiated. The concept of figure-ground separation is clearly demonstrated visually by the profile/vase illusion (Rubin, 1915). The limitation must occur to some extent at a central stage, as interference is also found when one message is visual and one is auditory and this reflects our limited attention capacity (Treisman, 1964). Attention is required to produce figure-ground segregation. Processing capacity is allocated to the figure, and leaves the ground relatively undifferentiated. In complex or difficult auditory environments, attention mechanisms enhance the processing of relevant auditory inputs, and suppress those that are irrelevant (Eramudugolla et al., 2005). Unattended stimuli will be ignored depending on the level of perceptual expertise the subject already has in the stimulus (Ruz et al., 2005). The extremely emotional context of disabling tinnitus might lead to a higher level of selective attention directed toward the tinnitus signal; increasing distress and preventing adaptive responses.

The activation of attention and cognitive networks may contribute to the annoyance and the inability to habituate to tinnitus (Zenner and Zala-man, 2004). Impaired concentration and reduced ability to undertake cognitively demanding tasks are frequently reported by tinnitus patients. Evidence from several recent studies (Andersson, 2002; Hallam et al., 2004) supports these reports. Hallam et al. (2004) proposed that tasks requiring switching of attention would be difficult for tinnitus sufferers and demonstrated that, compared to a non-tinnitus group, tinnitus sufferers showed a clear difficulty in inhibiting activity in a dual task reaction time test. Jacobson et al. (1996) suggested that if selective attention is increased by the

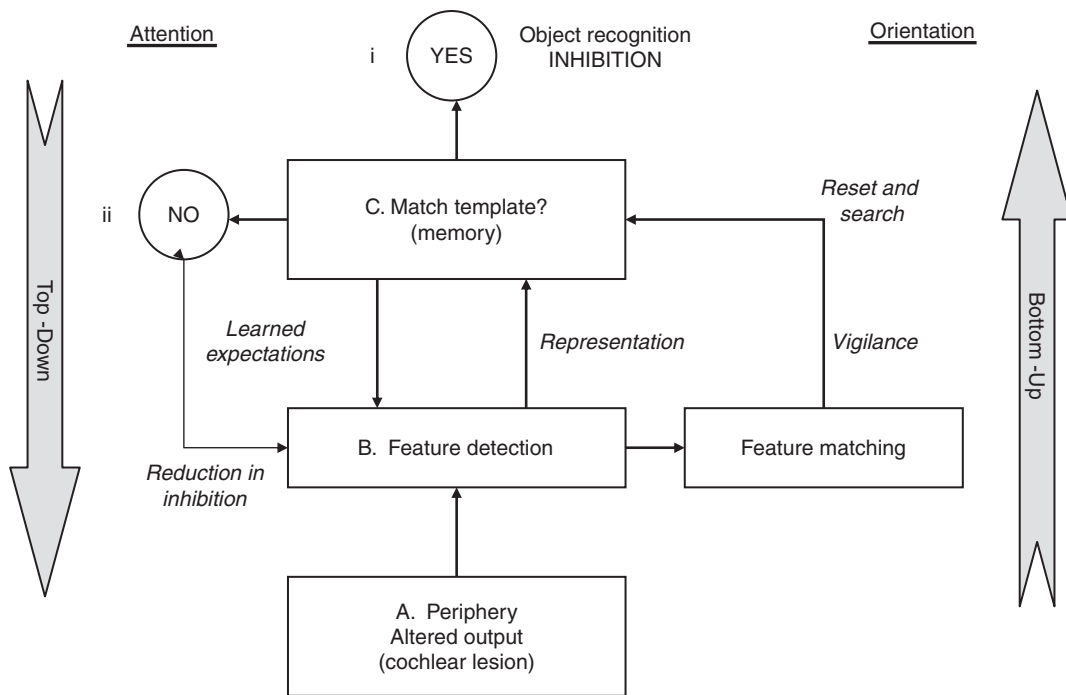


Fig. 1. A flow chart summarizing our model of tinnitus (chart based on Grossberg, 2000, p. 590). The figure attempts to summarize how departure of tinnitus from normal sound may lead to its annoyance and resistance to habituation. (A) Peripheral injury and consequent change to discharge patterns from the cochlea and auditory nerve. (B) Feature detection and representation according to Gestalt-like principles. (C) Encoding in short-term memory and matching of “normal” auditory patterns, (i) if the input activity matches pre-existing templates and is not changing the signal is inhibited, (ii) if there is a large mismatch a memory search for a more appropriate template occurs. Failure to match a template may lead to the persistence of the tinnitus.

continuous presence of bothersome tinnitus, an automatic attention bias may begin to occur, resulting from listening to the continuous internally generated sound. Other studies seem to confirm this; Goodwin and Johnson, (1980) compared reaction times (RTs) to auditory stimuli in normal hearing (without tinnitus) and hearing-impaired (with tinnitus) individuals. RTs to auditory stimuli in the tinnitus group were significantly shorter at the tinnitus frequency suggesting some kind of cognitive enhancement of the tinnitus-linked neural signal processing. A study by Cuny et al. (2004) has provided evidence for an automatic direction of attention toward the tinnitus ear (in cases of unilateral tinnitus). Involuntary attention shifts may be affected by the processing of the tinnitus signal, as individuals with tinnitus seem to have more difficulty redirecting their attention to something,

which is not their tinnitus — including a sound that simulates the person’s tinnitus. The presence of real tinnitus might direct attention automatically to the tinnitus ear and this direction of attention affects an automatically operating “deviance detection system” (Schroger, 1997). This “attention capture” effect was also proposed to reflect an ability of the CNS to detect inconsistency within a set of stimuli and to direct information processing automatically toward the deviant stimulus. Cuny et al. (2004) feel that this supports the hypothesis that the attention system does not allow the tinnitus signal to be classified as irrelevant information. Such a mechanism is similar to models proposed to explain how auditory hallucinations may arise from changed peripheral activity (Grossberg, 2000).

It has become increasingly clear that all areas of the brains of primates (including humans)

maintain a high degree of plasticity, even into adulthood and brain function can alter with training (Buonomano and Mersenich, 1998; Syka, 2002). Therapies using sound and training attempt to use this plasticity to their advantage by modifying brain function. Attention training is based on the premise that attention abilities can be improved by activating particular aspects of attention through a stimulus-drill approach. It is thought that repeatedly stimulating attention systems via graded attention exercises will promote changes in attention functioning (Sohlberg and Mateer, 1987) and lead to plastic changes in the brain. Such structured attention training oriented programs have been designed for treatment of patients with attention deficits such as can accompany acquired brain injuries (Sohlberg and Mateer, 1987) and schizophrenia (Lopez-Luengo and Vazquez, 2003). Although it is well accepted that tinnitus and auditory hallucinations are very different experiences, poor concentration, and inability to ignore the phantom sounds accompany both (Johns et al., 2002; Behrendt and Young, 2004). Therefore, an effective treatment might address problems common to both tinnitus and schizophrenia. The Attention Process Training (APT) program developed by Sohlberg and Mateer (1987) is a cognitive rehabilitation program originally designed to remediate attention deficits in individuals with brain injury. The APT materials consist of a group of tasks that exercise different components of attention commonly impaired after brain injury including: sustained, selective, alternating, and divided attention. The program tasks place increasing demands on complex attention control and working memory systems. Exercises include listening for descending number sequences, alphabetizing words in an orally presented sentence, and detecting targets with the presence of distracter noise. The use of APT in patients with specific brain injury has led to improvements in executive attention that have been reported to generalize to tasks remote from the training tasks (Rueda et al., 2005). APT has also proven to be successful in training attention abilities in children with ADHD (Kerns et al., 1999). Attention training appears to be most effective when directed at improving the subject's

performance on complex, functional tasks (Robinson and Summerfield, 1996).

Hatashita-Wong and Silverstein (2003) described a program for treatment of attention deficit disorders — based on principles similar to APT (increasing attention load) — for a patient who had attention deficits co-existing with auditory hallucinations. This therapy is intended to enable disattention (increased ignoring) of abnormal perceptions. A dichotic listening paradigm was recorded on audiotape; during playback the patient practiced attending to a target stimulus while ignoring irrelevant information at different spatial locations. Difficulty of task was increased as performance improved. After training the client was able to resist distraction to internal stimuli and had an increased ability to stay on-task (Hatashita-Wong and Silverstein, 2003).

Traditionally, in tinnitus therapy, sound has been used in a passive, non-attended manner to mask or facilitate habituation to tinnitus (Henry et al., 2002). Active auditory discrimination training listening tasks have recently been trialed as a component of therapies for tinnitus with some success (Flor et al., 2004). Flor et al (2004) found an effect regardless of the frequency of the tinnitus or the frequencies of sounds discriminated. Instead, treatment success was best predicted by the amount of regular training undertaken by individuals and psychological variables. These results suggest that the reduction in tinnitus associated with pitch discrimination tasks may be the consequence of attention mechanisms rather than frequency-specific reorganization (Brown et al., 2004).

In the present study, described below, persons with tinnitus were provided with training tasks, which involved actively focusing auditory attention on specific auditory objects and locations, while ignoring simultaneous background noise. In a review of auditory learning and training in adults, Robinson and Summerfield (1996) argue that three principles of learning are relevant for auditory training: (1) the more complex the task the longer the training period; (2) the greater the similarity between training and test tasks the greater the transfer, and (3) The more the training represents the variability of the auditory object

of interest (e.g., speech or tinnitus) the greater the transfer to everyday life (Robinson and Summerfield, 1996). As our goal was to train tinnitus patients to hear environmental sounds instead of their tinnitus, the training task required auditory object identification and location; rather than simple sound discrimination. It was hypothesized that after participants had undergone a short period of auditory attention training, they would be able to direct their auditory attention to exogenous/environmental auditory objects more easily, and more automatically, than prior to training. It was also hypothesized that the training would reduce their tinnitus awareness by enabling focus of attention on sounds other than tinnitus.

The specific aims of this study were to determine if auditory attention training could induce subjective changes in tinnitus minimum masking levels (MMLs) and pitch-matched tinnitus loudness levels (TLLs), and attempt to correlate any changes with changes in measures of attention.

Methods

This study was approved by the University of Auckland Human Participants Ethics Committee

on 15th of June 2006 (reference 2006/137). Subject data was recorded using Microsoft Excel 2003, and the statistical analysis was performed using SAS System 9.1.

Participants

Ten individuals (3 male, 7 female) mean age of 56.9 (SD = 5 years, range 46–62) with annoying tinnitus [mean Tinnitus Handicap Questionnaire (Kuk et al., 1990) score 40/100] were recruited through The University of Auckland's Hearing and Tinnitus Clinic. Participants had normal hearing (pure tone thresholds ≤ 20 dB HL) at 250 Hz and 500 Hz and hearing loss to varying degrees at higher frequencies (Fig. 2). No counseling addressing participants' tinnitus complaint or management was provided during the experimental period.

Hearing and tinnitus assessment

Testing was performed in a sound-attenuated booth (ANSI S3.1-1999). Air and bone conduction thresholds, TP, pitch-matched TLLs, and MMLs were obtained using a Grason-Stadler

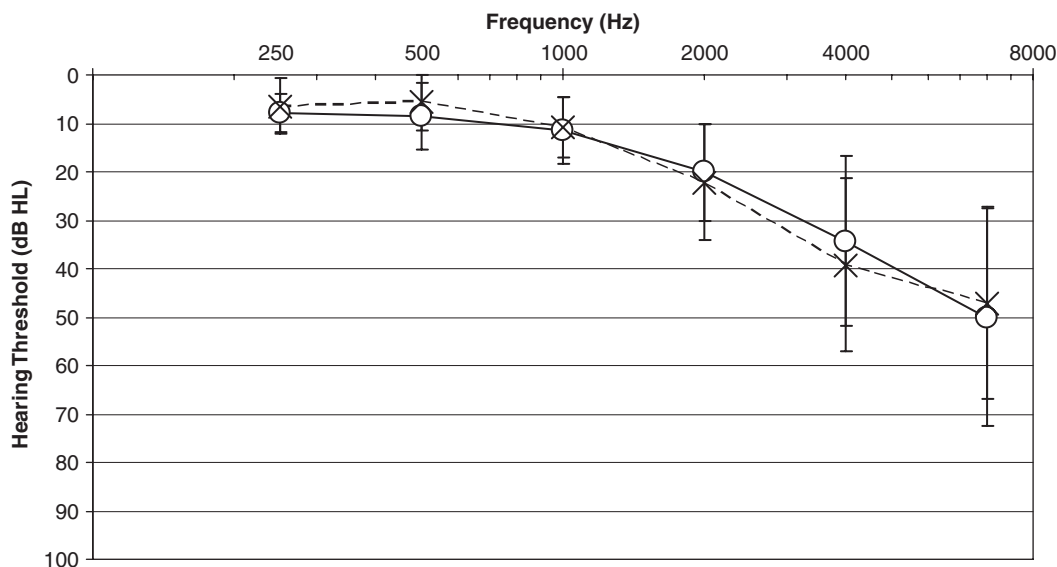


Fig. 2. Average hearing thresholds 250–8000 Hz for study participants (circle — right; cross — left ear) showing standard deviations at each frequency.

(GSI) 61 clinical audiometer, with Telephonics TDH 50P supraaural earphones. Sennheiser HAD 200 circumaural earphones were used for testing frequencies of 8–16 kHz. TP (1/2 octave spacing) was assessed using a two-alternative forced choice method at 10 dB sensation level and TLLs were obtained using an ascending method in 1 dB steps; MML was obtained with a narrow band noise (NBN; 0.5, 1, 2, 4, 8 kHz center frequency) stimulus. The MML for each frequency tested was defined as the sensation level that masked the tinnitus for two out of three repeats.

Attention assessment

Comprehensive attention batteryTM (CAB); (Rodenbough, 2003) Software version 5 was installed on a Dell Optiplex GX280 computer. This program was viewed via a Philips 105S monitor with a Magic Touch Keytech touch screen for participant responses. Auditory stimuli and CAB instructions were presented via two Harman/Kardon speakers. The CAB test was conducted with participants seated comfortably in front of the touch-sensitive screen attached to the computer monitor. Instructions were given verbally and a written form was also provided for participants to consult during testing to remind them how to use the program. If problems were encountered, such as the participant having difficulty understanding a test procedure then the “escape” key was pressed, and the interrupted individual test resumed from its beginning. The program automatically deleted the incomplete test once “escape” was hit. Participants listened to, and watched a demonstration tutorial before each test was run, and if required, practiced each type of test before the test itself was run. The CAB tests investigated in this study were the Auditory-Visual Multiprocessing Test, Auditory/Visual Discriminate Reaction Time Test, and Stroop Interference Cancellation Test (SICT).

Auditory-Visual Multiprocessing Test

This test was divided into two components — selective measurement of visual RT and auditory

RT. There were 40 trials for each modality. The stimuli were presented with random intervals between 1 and 4 s. For the two tests, each participant was presented with a gray square in the center of the screen that was approximately 200 mm wide and 180 mm tall. For the Visual Reaction Time Test each participant was instructed to touch the center gray square as quickly as possible whenever they saw a green flash (200 ms duration).

In the Auditory Reaction Time Test the participant was asked to touch the center square as quickly as possible after they heard a tone. The duration of the tone was 200 ms. In a similar way to the visual stimuli the tones occurred with random delays between 1 and 4 s. The Accuracy Scores obtained from this measure included the number of hits (correct responses) the percent of hits, number of multiple responses, unrelated (false) responses (<200 ms after stimulus), and failures to respond. Response Time Scores were derived from the mean RTs for hits and the standard deviation for RTs of hits.

Auditory/Visual Discriminate Reaction Time Test

Auditory and Visual tasks of the CAB had 70 stimuli with 35 targets and the shift task had 90 stimuli with 30 targets (stimulus duration: visual = 200 ms and auditory = 300 ms; inter-stimulus interval = 1800 ms). For the Visual Discriminate Reaction Time Test each participant was presented with a gray square in the center of the screen as described previously. Each participant was instructed to touch the center gray square as quickly as they could whenever they saw it flash red and not when it flashed either blue or green. These “flashes” lasted 200 ms and were presented with intervals of 1800 ms. The red, green, or blue flashes were presented in a random fashion with 35 targets (red flashes) and 35 non-targets (green or blue flashes). The Auditory Discriminate Reaction Time Test (DRTa) was very similar to the Visual Reaction Time Test. The only difference was that instead of the center square flashing red, green, or blue, the participants were presented with auditory stimuli consisting of the words “red”, “green”, or “blue”. Each participant was instructed to touch

the center gray square whenever they heard the word “green”; not when they heard either “red” or “blue”. The duration of the word presentation was approximately 300 ms. The target word (green) and the non-targets (red or blue) were presented 35 times in a pseudo-random fashion with each task lasting approximately 2.5 min.

The Shift Discriminate Reaction Time Test (DRTs) was similar to the Visual and DRTa. However, at different times during the test the participants were given the instruction “The Target Is.” The participants were then presented with either a red, green, or blue square flashing above the center gray square or they heard one of the words “red”, “green”, or “blue”. The participants were instructed to touch the center gray square as fast as they could whenever they saw or heard or viewed the target. During this task the target was changed seven times (signaled by the words “*The Target Is*”). Fifteen stimuli were presented, 5 of which were targets and 10 were non-targets. The targets change between colors and words. The 10 non-targets within each sub-trial were either color words or color flashes presented in a random fashion. This task lasted approximately 4 min.

Stroop Interference Cancellation Test

During the SICT of the CAB a screen appeared for 15 s. A total of eight screens were presented one after the other. Each participant was instructed to get as far as possible on each screen then restart the process when a new screen appeared. The participants were also instructed to touch every square where the color word (red, green, or blue) matched the color it was printed in and they were to touch as many squares as they could in the 15 s allowed. Then the screen automatically cleared and a new screen appeared; the participants continued the same task. This process occurred for four successive screens. For the next four screens, which appeared in successive fashion, the computer started playing the words “red”, “green”, or “blue” in a random fashion, once every second. The participants were instructed to continue the same process during this auditory distraction and their performance provided information regarding

focus-execute abilities and the ability to avoid auditory interference during a demanding visual task (Rodenbough, 2003). The Accuracy scores obtained from this measure included the number of hits (correct responses), percent hits, number of misses (incorrect responses), percent misses, and omissions (failure to respond).

Auditory training

The Auditory Object Identification and Localization (AOIL) task (The University of Auckland) was used for auditory training. The AOIL was loaded as specially designed MP3 format compressed sound files on PalmOne Tungsten E2 Personal Digital Assistants (PDAs) with Realplayer for PalmOne. Sony Stereo MDR-J20 headphones were used to present the sound. The participants were given the PDA’s to take home for their training. Chargers (Phihong PSMO3R-055P) were provided with each PDA to ensure the device would run for the duration of the trial. Each participant was instructed in the operation of the PDA, and given practice in operating it by themselves. A sheet with more detailed explanations and a diagram of the PDA and its operation was also provided. The positioning of the earphones was demonstrated to the participants.

Pictures of the most common 20 auditory objects used in the training, appearing in order on a single sheet, were shown to the participants while they listened to an audio CD played on a laptop computer (Dell Latitude). The purpose of this was to familiarize participants with the most common sounds, and reduce confusion and unfamiliarity. Participants identified each object in sequence as each noise was played on the CD, and familiarized themselves with these 20 sounds. The auditory objects were: horse neighing; fax modem; squeaky toy; zip; neon sign; bite/crunch; power drill; ice cubes in glass; jet airplane; cat meow; jackhammer; storm/arc welder; train; whale song; truck; wrench; creaking door; shaver; frog; vacuum cleaner. The first day’s training consisted of identifying these sounds only.

After familiarization, the participants were given the PDAs to take home and instructed to

undertake the AOIL tasks for approximately 30 min/day, over a period of 15 days. The AOIL sounds were grouped in threes (a “triplet”); one entering the left ear, one entering the right ear, and one entering both ears simultaneously (and giving the impression of central auditory perception). Apart from day 1, background noise of various types was superimposed on the sound files.

From day 1 to 10, 20 listening tasks were undertaken per day. A male voice giving auditory instructions were included in the sound files, at the beginning of day 1 and day 2; and thereafter a background noise to be ignored was identified by the same male voice. From day 1 onwards, additional common sounds (such as water running, owl hooting, coughing, dogs barking, bees buzzing, etc.) were also introduced, alongside the already-familiar sounds. In addition — from day 2 onwards — these sounds were heard; had to be identified and located against a background of noise (such as a fax modem, traffic, multi-talker babble). Up to day 10 the three sounds to be identified occurred in sequence. From day 10 they either overlapped or occurred simultaneously. The final task (day 15) required the participants to identify particular words heard against a multi-talker background. The words were identified before the task began, so that participants knew what to listen for. From day 10 on, 15 tasks per day were undertaken.

Each listening task required the participants to recognize, identify, and write down the auditory object that was heard. The words indicating the object sound were to be written in a box printed on a sheet of paper. Each box was divided into three parts: spatially representing “left”, “right”, and “center”. Participants had to write the sound they heard in the spatial location representing the location they had identified the sound as coming from through their headphones (left, right, or both headphones).

Participants were asked to listen to each day’s tasks and identify in writing the names of each object in the triplets, in the spaces provided for the relevant day and task number. Participants could pause the recording and repeat it using the appropriate buttons, listening to each task as many times as they needed to, in order to identify the sounds, and their locations (left, right, or center). They

were asked to mark in a tally box the number of times they listened to each triplet before feeling confident about its identity.

The participants were asked to complete the training within 3 weeks or a minimum of 15 days. They were asked not to do more than one day’s training per day; told that each day’s training was expected to take from between 20 and 30 min; but could take as much time as they needed. Participants were encouraged to contact the experimenter if any problems arose. When a problem did arise, the experimenter talked through the problem on the telephone; if this was insufficient, the participant was visited by the experimenter in his or her home in order to rectify the problem.

Results

The characteristics of the participants prior to training are summarized in Table 1. Individual tinnitus pitch-match ranged from 0.5 to 12 kHz and tinnitus loudness was 10 dB SL ($SD = 5$). MMLs centered closest to TP varied from just above 12 to 46 dB SL, MMLs were generally low- to high-frequency NBN (not shown).

Seven of the 10 participants had a reduction in their pitch-matched TLL following training (Fig. 3 and Table 2). Two of the participants (B.B. and D.J.) displayed no change in loudness levels after training. One participant’s (C.H.) pitch-matched loudness levels increased after training. Excluding this participant, the average loudness level of the tinnitus (for nine participants) was reduced by 6 dB SL. However, the mean change in tinnitus loudness after training was not statistically significant ($t(8) = 0.13$, $p = 0.9$).

There was a reduction in MML at the frequency closest to individual tinnitus pitch-matches in 8 out of 10 participants (Fig. 4 and Table 2). In two participants (BB and CH) there was an increase in pitch-matched MMLs. The MML was reduced to all NBN stimuli following training in 7 out of 10 participants (e.g., participant RL, Fig. 5). Pitch-matched MMLs were significantly lower after training [$t(8) = 3.53$, $p < 0.01$].

The Discriminate Reaction Time Test was a focused attention task with continually changing

Table 1. Individual participant tinnitus characteristics

Subjects	Age (years)	THQ (score/100)	Pitch match (Hz)	Loudness (dB SL)	MML (dB SL)
B.B.	61	50	6000	8	12
C.H.	52	23	8000	8	39
D.J.	62	39	8000	6	12
R.L.	62	49	8000	10	46
C.M.	58	27	4000	16	16
V.N.	46	51	12,000	12	17
C.O.	59	57	6000	6	26
V.R.	56	31	8000	14	35
K.T.	55	43	12,000	5	22
D.C.	58	33	500	18	36
Mean	57	40	7250	10	26
SD	5	11	3442	5	12

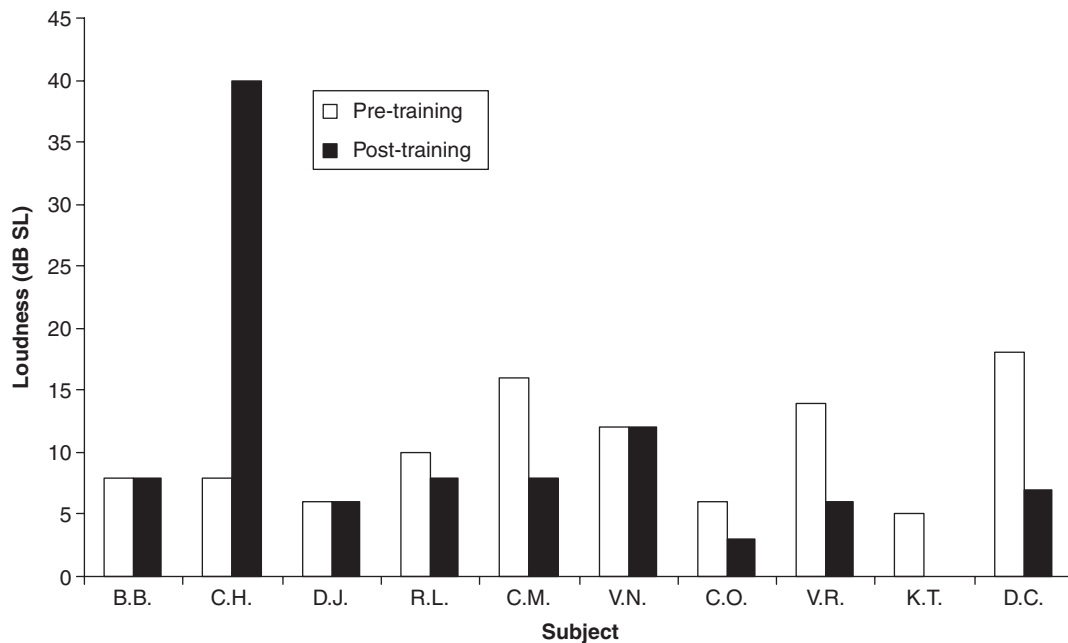


Fig. 3. Pitch-matched tinnitus loudness levels, across subjects, before (open bars) and after (black) training. Subject K.T.'s TLL was 0 dB SL post-training (threshold and pitch-matched loudness levels were the same).

(“mixed”) targets of different sensory channels. For example, the target may have been a flash of the color red and a non-target may have been the word “red”. An assumption is made that the shift task reflects an abstract capacity to shift from attending to one aspect or stimulus feature of the target to another in an adaptive manner (Rodenbough, 2003). Nine participants had an increase

(improvement) in the number of hits following training. Two participants (B.B. and V.N.) had the smallest increase in number of hits post-training in this measure and one participant CH had no change. There were no significant changes after training in the number of hits on the DRTa. Three participants (R.L., D.C., and K.T.) had particular difficulties on the Auditory and Visual (DRTs)

Table 2. Relationship between tinnitus and attention measures

Subjects	Increase in number of hits DRTs task	Change in RT total (ms) post-training (+ ve faster, -ve slower)	Degree of change MMLs (dB SL)	Degree of change loudness levels (dB SL)
B.B.	2	+16	+2	0
C.H.	0	+431	+5	+32
D.J.	3	+116	-4	0
R.L.	15	+160	-31	-2
C.M.	5	+47	-8	-8
V.N.	1	+0	-11	0
C.O.	14	-10	-20	-3
V.R.	8	-15	-21	-8
K.T.	6	-39	-20	-5
D.C.	22	+70	-24	-11

Notes: Comparison of change in DRTs hits; SCIT RTs; MML; and TLL with the AOIL training task. A negative value indicates a reduction (improvement) in the tinnitus measures.

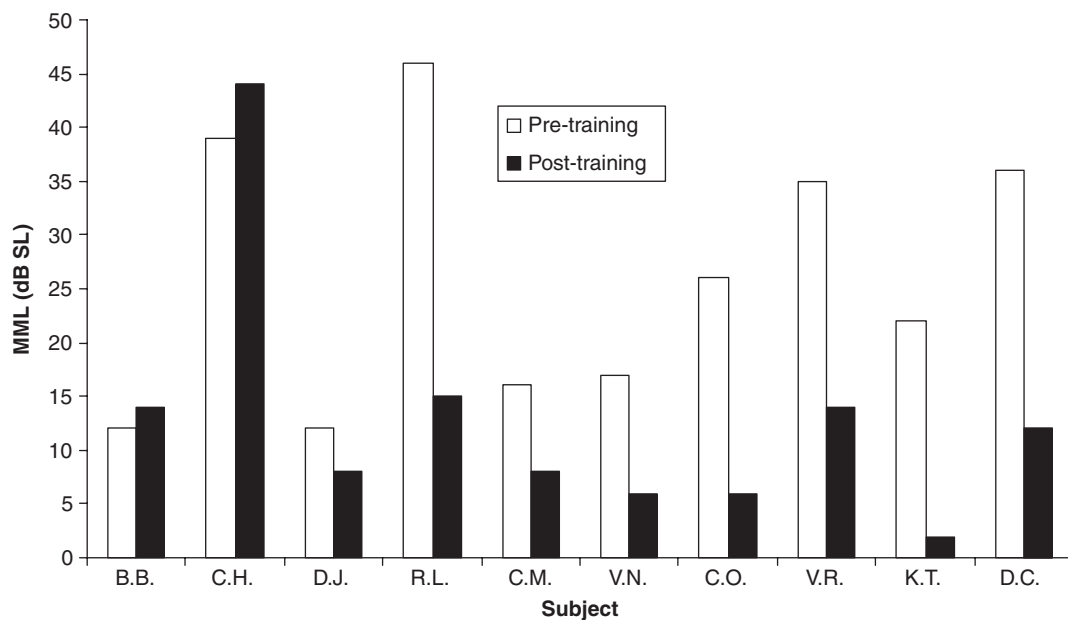


Fig. 4. Individual pre-training (open bars) and post-training (black) MMLs in dB SL at closest narrow-band noise frequency to tinnitus pitch-match for each participant.

part of this task; they required the permitted practice (tutorial) section and instructions to be repeated seven or eight times. Overall, participants (with tinnitus) seemed to find it extremely difficult to separate the auditory from the visual cues and to hold a memory of what each temporary target was.

There was little or no change in the simple Visual Reaction Time Test and the simple Auditory Reaction Time Test following AOIL training; with no apparent procedural learning effect on retesting after 3 weeks. The Shift Discriminate Reaction Time Test showed an improvement in nine

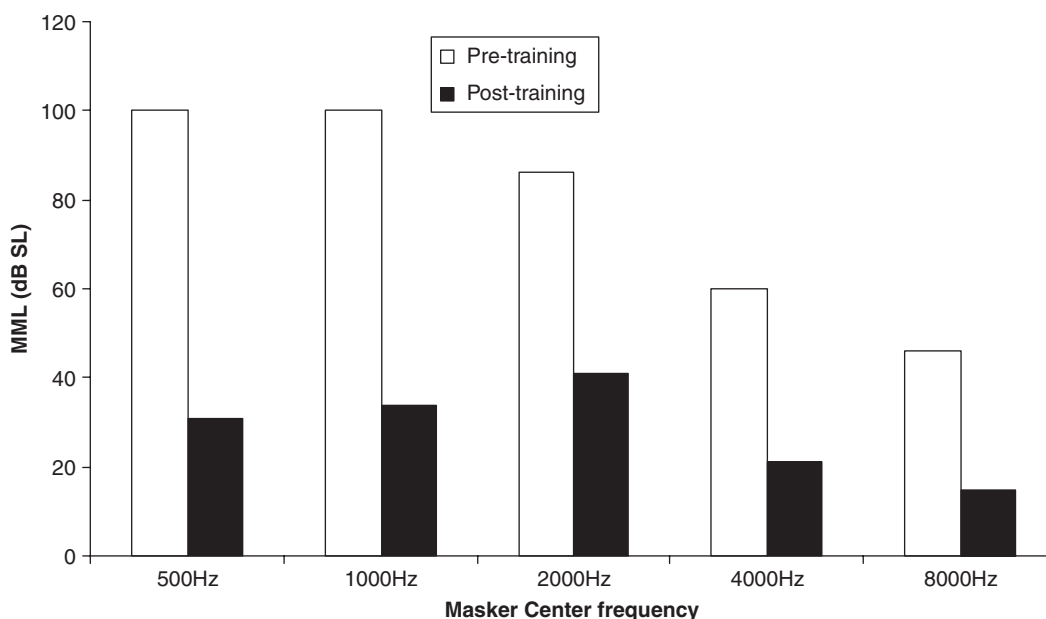


Fig. 5. Participant R.L.'s MMLs from 0.5 to 8 kHz, pre-training (open bars) and post-training (black).

participants. Two of the largest improvements were seen in participants C.O. (+14) and D.C. (+22). These participants had relatively large changes in MMLs and loudness levels post-training. Three participants (B.B., D.J., and V.N.) had only a small increase in the number of hits (from 1 to +3) in the DRTs task; they had no change in TLLs.

The DRTs is a measure of the ability to shift focused attention between cues. A skill which many individuals with tinnitus would be expected to have difficulty with because it expected that tinnitus occupies some of the (auditory) attention resources available to individuals. There was no statistically significant (analysis of variance, ANOVA) difference, before and after training, on the DRTs attention measure and pitch-matched TLLs ($F(1, 8) = 3.04$, $p = 0.12$) (Fig. 6), but there was strong evidence that a relationship existed between the change in the DRTs measures, and the change in the MML measures across individuals ($F(1, 8) = 14.5$, $p < 0.005$) (Fig. 7).

The SICT is a test of focused attention and it includes both distraction and response interference during the final auditory interference component of this test. The auditory component is illustrated

before and after training (Fig. 8). One participant (D.C.) attempted the SICT three times (auditory interference component), but found he could not cope with the auditory distracter, and gave up on his third attempt.

On the CAB test, two participants had slow pure mean auditory RTs before training, compared to normal values of pure auditory RT times (B.B.: +105 and C.H.: +418 ms). The same two participants had small increases in tinnitus pitch-matched MMLs post-auditory attention training (+2 and +5 dB SL, respectively). All other eight participants experienced a decrease in MMLs, ranging from -4 dB SL to -31 dB SL (Table 2). The participant with the smallest drop in MML post-training (D.J.) also had a relatively large auditory RT pre-training (+68 ms).

The relationship between the post-training change in individual RT and changes in pitch-matched TLLs was significant (ANOVA: $F(1, 8) = 23.98$, $p < 0.001$) (Fig. 9). No statistical relationship was found between the changes in size of individual RT following training and changes in the size of pitch-matched MLLs ($F(1, 8) = 224.40$, $p = 0.2$) (Fig. 10).

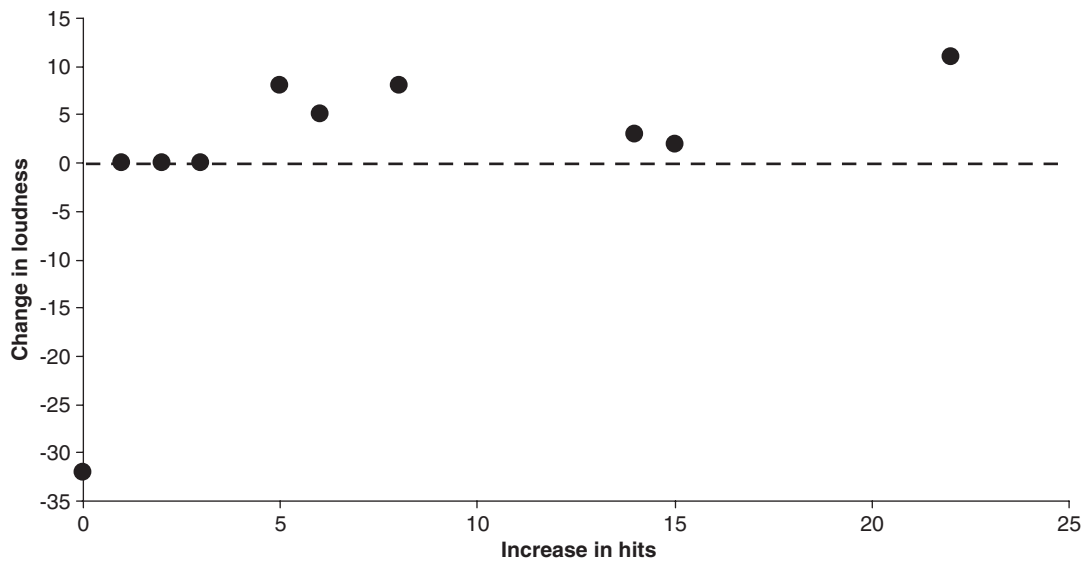


Fig. 6. The amount of change in pitch-matched loudness levels as a function of the amount of change (number of hits) in the shift component of the Discriminate Reaction Time Test following training. No relationship was shown statistically between the DRTs attention measure and pitch-matched tinnitus loudness levels.

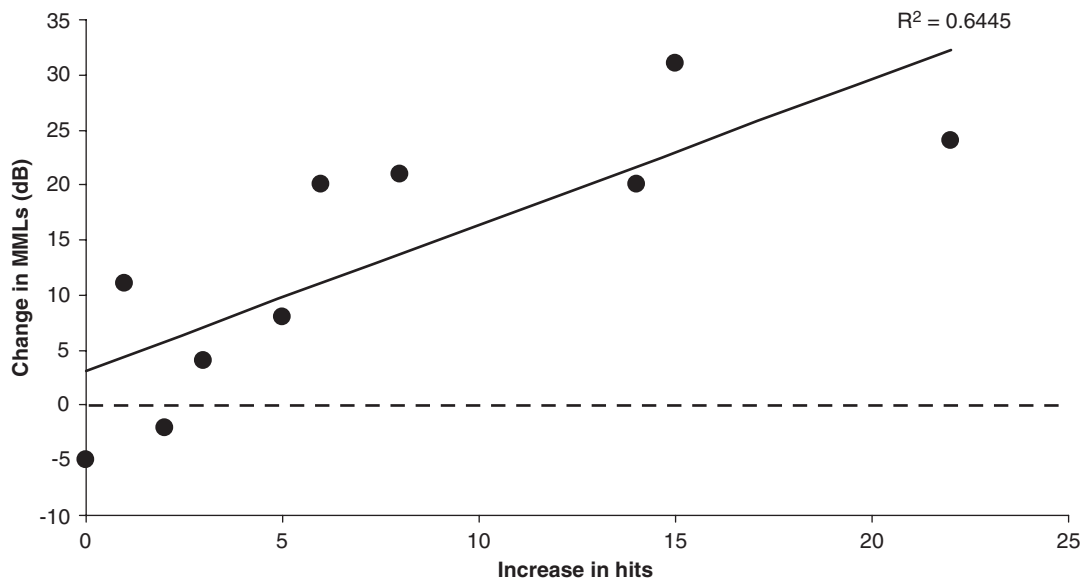


Fig. 7. The amount of change in the pitch-matched minimum masking levels as a function of the change (number of hits) in the DRTs following training. The results showed strong evidence that there was a relationship between the change in the DRTs measures and the change in the MML measures across individuals.

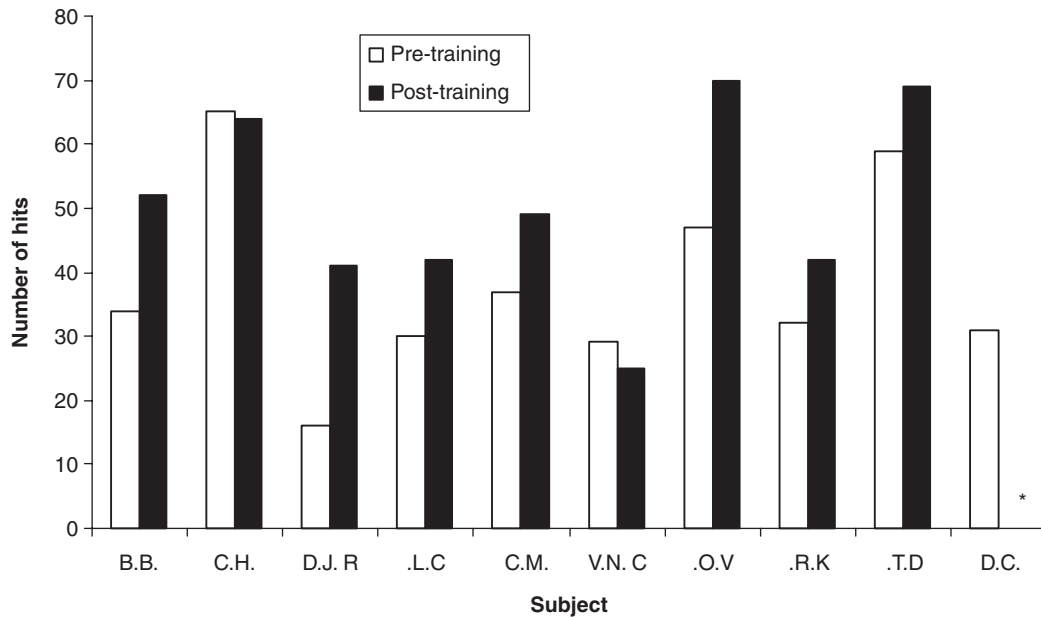


Fig. 8. Auditory interference component of the Stroop Interference Cancellation Test (SICT) before and after training for each participant. *Participant D.C. attempted the auditory interference component of the SICT three times, but found he could not cope with the auditory distracter, and gave up on his third attempt.

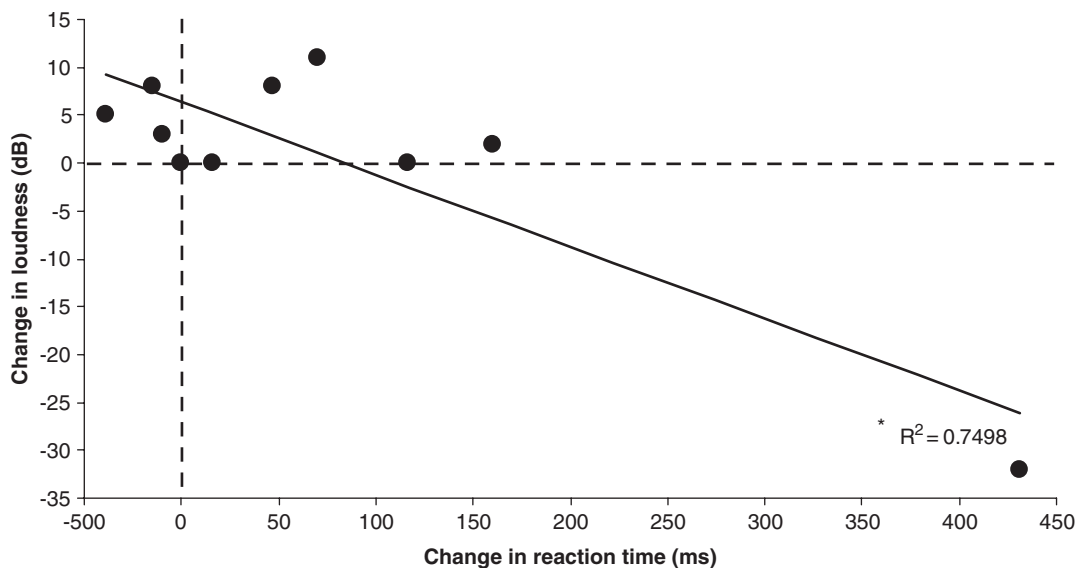


Fig. 9. Changes in pitch-matched tinnitus loudness levels following training as a function change in individual RTs. *The correlation should be interpreted with caution due to the potential biasing of results by a single participant.

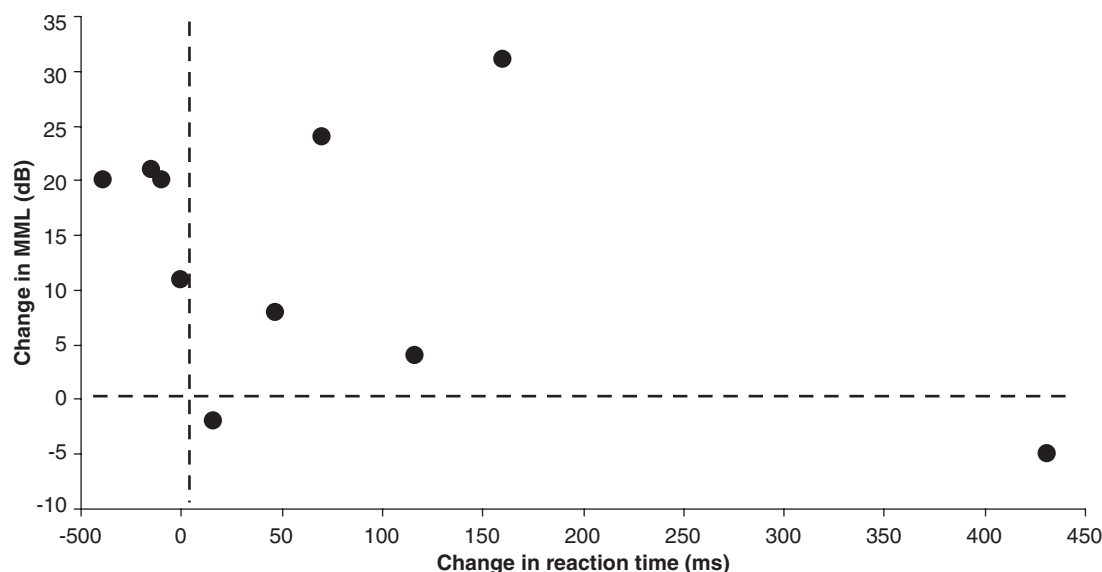


Fig. 10. Changes in the size of pitch-matched MLLs as a function of changes in size of individual RTs, following training.

Discussion

The way people perceive their tinnitus is a significant contributor to tinnitus severity and to the difficulties to habituate to it (Zenner and Zalaman, 2004). We have presented a model of tinnitus cognition, which incorporates tinnitus within concepts of scene analysis and attention. We believe that the difference between ASA of normal sound and tinnitus inhibits habituation. This study showed that training to improve attention to auditory objects, other than tinnitus can reduce tinnitus audibility in some people after a short period of time (15 days).

The results of the present study show a strong relationship between improvements post-training in the focused switching of attention required for the DRTs test and a decrease in the amount of masking required to just cover the tinnitus sound. The implication is that the training may have enabled individuals with tinnitus to switch attention away from the tinnitus and pay more attention to masking sounds, so that the tinnitus was covered at lower intensities of masker than would have been the case without the training.

There is now considerable evidence that sensory perception is multimodal and unimodal processing exist only at relatively early sensory processing

stages of classical sensory pathways up to and including primary sensory cortices. Non-classical pathways that bypasses primary cortices and for example neurons in nuclei in the ascending auditory pathways respond also to other sensory modalities (Møller, 2003). There are indications that the non-classical (extralemniscal) pathways are active in some individuals with tinnitus (Møller et al., 1992) [and in children (Møller and Rollins, 2002)]. There are other indications that the abnormal neural activity that cause tinnitus is not generated in the same neural structures that are involved in processing sounds (Lockwood et al., 1998).

The results of the present study suggests that ultimately, in a fully-realized end-user version of an auditory attention-training program, it might be useful to incorporate a multimodal approach, so that as well as directing attention to useful sounds rather than tinnitus, trainees can learn to make fuller use of simultaneous inputs from various sensory modalities; plugging holes, as it were, in one damaged modality with increased attention to information from another modality. Attention training appears to be most effective when directed at improving the participant's performance on complex, functional tasks (Robinson and Sumnerfield, 1996). For this reason, and on the basis

of our model of tinnitus perception, choice of an AOIL task would appear suitable for tinnitus treatment.

Virtual reality (VR) technology may encourage and facilitate the use of the AOIL and allow incorporation of visual tasks. As an extension of the research report described above we plan to develop cross modality distracters to train the auditory system to attend to normal auditory and visual activity instead of tinnitus. An element of competition and “playability” may facilitate patient compliance as well as accelerate training effects. Training with video games has been shown to produce better performance on a variety of visual attention tasks (Green and Bavelier, 2003). Green and Bavelier (2003) hypothesized that video game players have increased capacity of the visual attention system, compared to non-video game players and that this is caused by the training effect of frequently playing the video games. Video game players exhaust their visual attention resources more slowly than non-video game players in the face of distracters, and have an increased field of view. In addition, video game training appears to enhance task-switching abilities as well as decreasing attentional blink (the difficulty in processing a target that comes a few hundreds of milliseconds after an earlier target). Furthermore, when non-players are trained on an action video game, they too, show a significant increase in their visual attention abilities. Green and Bavelier (2003) suggest that forcing players to simultaneously juggle a number of differing tasks (including detecting new enemies, tracking existing enemies, and avoiding getting “hurt”) enhanced three different aspects of visual attention. This could be seen with detectable effects on new tasks and at untrained locations after only 10 days of training. They suggest that changes in known attention bottlenecks, as well as speeded perceptual processes and/or better management of several tasks at the central executive level, are likely to play a part in this improvement. It is also possible that the cross-modal effects discussed earlier, with simultaneous and reinforcing inputs from somatosensory, auditory as well as visual modalities, all play a part in increasing measurable performance effects following attention training. VR

technology enables the multisensory input of hearing, sight, and touch can enable people to feel part of a virtual world. VR and video games are beginning to be used in many health applications (Riva, 1997) and may, eventually, have a significant role in tinnitus management. The use of nerve growth factors and gene therapy, together with stimulation or training to develop appropriate neural networks may also, in the future, facilitate tinnitus reduction or elimination.

There are several difficulties inherent in studying tinnitus, attention and scene analysis together; each is multidimensional and can be influenced by factors such as age and psychological status, they are not independent of each other, and there is no consensus as to gold standard assessment measures. The present study had limitations; the model underlying the treatment approach is yet to be rigorously tested, few participants underwent treatment, a large number of factors potentially contributed to outcome, and outcomes were not compared to a control group. There were only 10 participants in this study; hence any individual variables might be expected to have an exaggerated effect. However, only one participant showed behavior opposite to the general trend (participant C.H.).

The tasks of the participants in the study contained several different elements: (1) attend to where the recorded sounds were coming from (left, right, or center), (2) identify the sounds, (3) ignore the background sound and attend to the sounds and locations demanded by the task. In this small study we have not attempted to determine which element of the training was responsible for the changes observed. We cannot determine whether attention or improved object identification was responsible for the observed reductions in MML and TLLs. In the study the treatment was not compared to an alternative or no treatment condition — but this is being addressed in a further trial. The authors are yet to determine whether any changes could be generalized to other situations, or were maintained over time. The length of training in the current study was relatively short (15 days), and a longer training may yield more significant results. A longitudinal blinded cross-over study is underway to investigate the training compared to counseling and conventional sound therapy. The

further trial will address many of the limitations of the present study. In addition, questions such as when training should be undertaken will be considered, as it has been shown that perceptual improvements following training can be enhanced if sleep follows training (Atienza et al., 2004).

Conclusion

The present study investigated the effects of a short, take-home auditory training program on psychoacoustic measures of tinnitus. MMLs and TLL were reduced in most participants following training — consistent with the hypothesis that a demanding auditory identification and localization-training task should improve identification of non-tinnitus auditory objects. The study supported the hypothesis that active training, which engages attention, may be effective in a shorter time than some current, passive, auditory training therapies aimed at alleviating tinnitus. The results of the study also suggested that the effect of training might be greater on pitch-matched tinnitus MMLs than on actual TLLs. The reasons for this are unclear, although a correlation found between changes in MMLs and improvements in the ability to shift attention is one possible reason.

On the basis of the results of the present study we suggest that AOIL should be used alongside with counseling (Henry and Wilson, 2001) and provision of hearing aids and music distraction (Searchfield, 2006) in the treatment of patients with tinnitus. The patients should be instructed that their task is to extract as much information about their auditory environment as possible. Patients can and should also make use of resources they already have, such as simple attention strategies (Henry and Wilson, 2001) and (through training) they should be encouraged to stretch their abilities to search and identify auditory objects other than tinnitus.

Abbreviations

ADHD Attention Deficit Hyperactivity Disorder

ANOVA	Analysis of Variance
AOIL	Auditory Object Identification and Localization
APT	Attention Process Training
ASA	Auditory Scene Analysis
CAB	Comprehensive Attention Battery
CNS	Central Nervous System
DRTa	Auditory Discriminate Reaction Time Test
DRTs	Shift Discriminate Reaction Time Test
MML	Minimum Masking Level
NBN	Narrow Band Noise
PDA	Personal Digital Assistant
RT	Reaction Time
SICT	Stroop Interference Cancellation Test
TLL	Tinnitus Loudness Level
TP	Tinnitus Pitch
VR	Virtual Reality

Acknowledgments

The authors are grateful to the Tinnitus Research Initiative (TRI) for funding our research. We thank Michael Sanders for his contribution in the development of the AOIL.

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CHAPTER 44

Extinction training for tinnitus

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Abstract: Recent accounts of tinnitus development and maintenance assign an important role to central mechanisms. Residual inhibition is a frequent phenomenon in individuals with tinnitus, and refers to the fact that tinnitus can temporarily be reduced by presenting sounds or noises that inhibit tinnitus for a limited time even after termination of the sound. This kind of stimulation-induced inhibition of tinnitus could potentially be used for treatment by combining it with additional interventions to enhance the extinction of tinnitus. Here we propose a training program aimed at the amplification and the extension in time of residual inhibition as well as the extinction of negative emotional responses to the tinnitus. The program is tested alone or in combination with a pharmacological intervention that is aimed at decreasing central hyperactivity. Treatment effects are assessed by tinnitus questionnaires, electroencephalographic measures (reduction in the amplitude of the N₁₀₀ component of the event-related potential as an indicator of habituation) as well as skin conductance responses to 1000 Hz tones or tinnitus-like tones. This training is an example of the use of centrally acting and mechanism-oriented tinnitus treatments.

Keywords: tinnitus; extinction training; residual inhibition; pregabalin; EEG; N₁₀₀; skin conductance response

Introduction

Most of the interventions for tinnitus that are in use focus on the effects that tinnitus has on the individuals' lives (interference), but does not provide a mechanism-based and therefore causal intervention. The interventions that are commonly used include cognitive-behavioral approaches (Jastreboff and Jastreboff, 2000; Kroener-Herwig et al., 2000; Andersson, 2001) (see Chapters 40 and 41), which have shown positive effects on the interference related to tinnitus. Many recent studies on central processing in tinnitus suggest that tinnitus is associated with central hyperactivity

(see Chapter 1, 2, and 6). An influential model of tinnitus generation and maintenance by Jastreboff et al. (1996) postulated plastic changes that involve alterations in and close interactions among limbic, auditory, and associated cortical brain areas. Several imaging studies showed, in fact, abnormally increased activity in auditory cortex and limbic regions in individuals with tinnitus (e.g., Arnold et al. 1996; Lockwood et al., 1999; Andersson et al., 2000; Diesch et al., 2004, 2007) and topographically similar activation in healthy controls listening to aversive noise (Mirz et al., 2000). The positron emission tomography (PET) study by Arnold et al. (1996) found that the increase of metabolic activity in the primary auditory cortex in individuals with tinnitus is positively correlated with tinnitus loudness, a

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correlation also reported by [Diesch et al. \(2004\)](#) for the amplitude of the auditory steady-state response measured by magnetoencephalography (MEG), [Mühlnickel et al. \(1998\)](#) for the deviation of the tonotopic map in MEG, and [Weisz et al. \(2005\)](#) for the auditory mismatch negativity potential. Several animal studies showed hyperactivity in subcortical structures from deprivation of input (e.g., [Gerken, 1996](#)). There is also evidence for generally increased central activity in individuals with chronic tinnitus: Using transcranial magnetic stimulation, [Langguth et al. \(2005\)](#) reported a significantly higher neuronal activity in motor areas related to reduced intracortical inhibition in individuals with tinnitus as compared to healthy controls. This kind of hyperactivity indicates reorganization that may contribute to lack of habituation and the development of chronic tinnitus. In chronic tinnitus, these plastic changes in the CNS and phenomena such as the expansion of receptive fields to include originally non-involved brain areas resemble phenomena associated with phantom limb pain (e.g., [Flor et al., 1995](#); [Mühlnickel et al., 1998](#); [Møller, 2001, 2006](#)) (see Chapters 1 and 4) and it has been suggested that similar mechanisms may be active in tinnitus ([Flor and Schwartz, 2003](#)). Interestingly, the correlation between tinnitus-related hyperactivity and tinnitus intensity and interference reported by [Diesch et al. \(2004\)](#) was present also after compensation for the degree of individual hearing loss was made. Thus methods that are suitable for reducing tinnitus-associated hyperactivity of the brain and increase inhibition might be promising for a mechanism-oriented treatment of tinnitus.

Several studies have demonstrated that masking sounds can lead to suppression of tinnitus for a period after termination of the sound exposure ([Feldmann, 1971](#)). This phenomenon is known as residual inhibition and is defined as the temporary diminution or complete suppression of an individual's tinnitus following the presentation of a masking sound. Residual inhibition seems to be correlated with the temporary threshold shift that occurs after exposure to loud sounds, the spectrum of which is within the range of the tinnitus ([Terry et al., 1983](#)) (see Chapter 47). Typically, residual inhibition lasts either a few seconds or a few

minutes, but occasionally it can persist substantially longer. [Hazell and Wood \(1981\)](#) reported several cases in which 15 min of noise resulted in residual inhibition of tinnitus for the entire day. However, the factors resulting in persistence of inhibition and the mechanisms are not well understood. [Tyler et al. \(1984\)](#) note that factors influencing residual inhibition include the duration of the noise as well as noise level. While [Terry et al. \(1983\)](#) did not find evidence for residual inhibition induced by contralateral masking, [Feldmann \(1971\)](#) and others did, which would support the hypothesis of central mechanisms underlying residual inhibition. Cochlear effects cannot solely explain residual inhibition because cochlear effects such as forward masking last for only several milliseconds.

Direct electrical stimulation of the cochlea as done by cochlear implants cause residual inhibition (e.g., [Ruckenstein et al., 2001](#)). Transtympanic electrical stimulation also evoked residual inhibition (e.g., [Rubinstein et al., 2003](#)). Evidence for central participation in residual inhibition has been presented by [Osaki et al. \(2005\)](#) who conducted a PET study on residual inhibition in cochlear implant users and found that the right anterior middle and superior temporal gyri (Brodmann areas 21 and 38) were activated during residual inhibition. There is evidence that the medial temporal lobe also is involved in residual auditory inhibition (e.g., [De Ridder et al., 2004](#)).

In an ongoing study we use induction of residual inhibition as a means to reduce tinnitus-associated central hyperactivity and thus, presumably, the experience of tinnitus in analogy with the provision of normalizing input in individuals with phantom limb pain ([Flor et al., 2001](#)). We attempt to enhance the effects of residual inhibition in extinction training where patients who are being treated for tinnitus are provided with auditory signals that induce residual inhibition and are trained to increase and extend its positive effects by employing imagery of the auditory stimulation. Imagery and illusory percepts are assumed to activate the same brain mechanisms as the actual percept (see e.g., [Husain et al., 2005](#) for auditory cortex) and this effect can be used in training.

Recently, combinations of pharmacological and behavioral interventions have been shown to be more effective in changing cortical maps than either one of these interventions alone (e.g., [Dinse et al., 2003](#)). This approach has been used in the treatment of acrophobia or social phobia where the combination of extinction training and administrations of the partial NMDA receptor agonist D-cycloserine yielded superior effects to virtual reality extinction training or in vivo exposure therapy alone ([Ressler et al., 2004](#); [Hofmann et al., 2006](#)). A drug that has been used to enhance behavioral interventions is pregabalin, which is a new substance that acts on the calcium channel and is similar to gabapentin (see Chapter 27).

Pregabalin (Lyrica[®]) exerts its effect by modulating voltage-gated calcium channels. Pregabalin has a linear pharmacokinetic profile. It is completely absorbed, not bound to plasma proteins, not metabolized, and eliminated unchanged through the kidneys. Doses must be adjusted in patients with renal insufficiency. Clinical trials showed that pregabalin is effective in neuropathic pain associated with postherpetic neuralgia, diabetic peripheral neuropathy, in partial epilepsy, and in generalized and social anxiety disorders (see [Pande et al., 2003](#); [Rosenstock et al., 2004](#)). The most common adverse effects were dizziness and somnolence. Few serious adverse effects were reported. It has so far mainly been used as analgesic, antiepileptic, and anxiolytic medication. Due to its effects on central hyperactivity, we believe that it should enhance the effects of tinnitus extinction training.

Main objectives

In the present study we use the phenomenon of residual inhibition as an interventional approach to the treatment of tinnitus, and we have implemented a training procedure that aims at maximizing the depth and duration of residual inhibition. Our aim is to enable persons with tinnitus to learn not to adapt to but to extinguish their sensation of tinnitus as well as the associated negative emotional response. In the current study we extend our previous training efforts ([Flor et al.,](#)

[2004](#)) and address general tinnitus-related hyperactivity by using administration of a centrally acting drug (pregabalin). The aim of using pregabalin is to decrease central hyperactivity. The effect of pregabalin is compared to the effect of a placebo.

The first objective of the study is to establish an extinction-training program for tinnitus that makes use of the fact that the provision of auditory input, natural or artificial, can lead to residual inhibition and thus cessation of the sensation of tinnitus for a certain time. We determine the optimal auditory signal that affects tinnitus and train chronic tinnitus sufferers to increase and extend the suppression of tinnitus over a training period of 2 months. This serves to promote habituation to the tinnitus and achieve its extinction via repeated noise presentation intended to activate residual inhibition. Moreover, the participants are instructed to extend the state of residual inhibition and thus obtain extinction of the perception of their tinnitus itself and the associated negative emotional responses (suffering).

Second, in half of the participants in the study administration of pregabalin is used to enhance the training effects, in the other half a placebo is given in a double-blind randomized fashion to test the additive effects of the calcium channel modulator on the training effects. Pregabalin has already been shown to be effective in the treatment of central neuropathic pain as well as in anxiety disorders by decreasing neural hyperactivity, it is also used as an anticonvulsant.

The subjective effects on tinnitus of this combination treatment is assessed by a diary, the response to several questionnaires on the impact of the tinnitus on daily life, and an assessment of tinnitus loudness pre, post, and 3 months after the training.

A final objective of the study is to determine central and peripheral correlates of tinnitus extinction. Habituation of the auditory N₁₀₀ potential in response to sounds, the frequency of which are in the range of the frequency of the participants' tinnitus as well as a standard 1000 Hz tone will be assessed as well as an indicator of autonomic reactivity, the stimulus-evoked change in skin conductance response in response to sound

stimulation. The long-term goal of the project is to develop a miniaturized training device for tinnitus sufferers. This training would have a direct effect on the sensation of tinnitus rather than the interference related to tinnitus.

Study design

We have assigned 28 individuals with chronic tinnitus to a training + pregabalin condition or to a training + placebo condition in a randomized double-blind fashion. This group design is combined with a multiple baseline design in which small groups of individuals with tinnitus successively enter treatment after 2, 4, 6, or 8 weeks of waiting, thus providing variable waiting periods that will be used to assess tinnitus parameters and that can be used to control for time effects (see Fig. 1 for

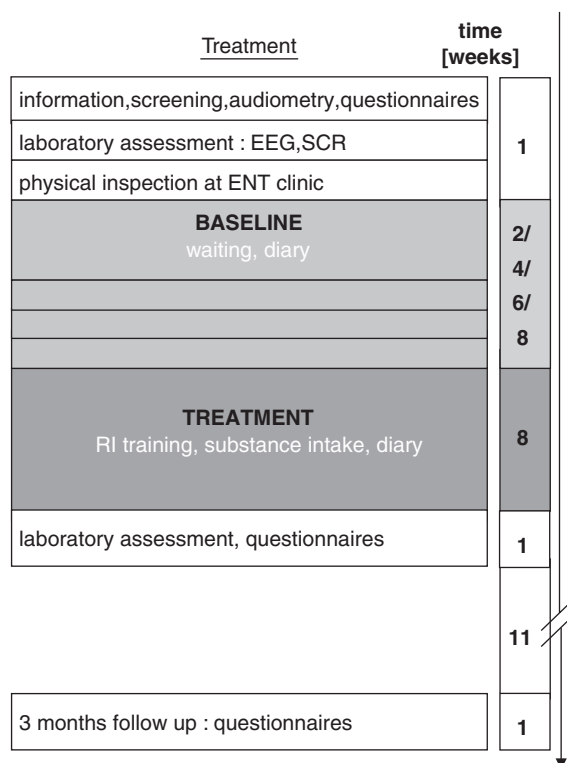


Fig. 1. Outline of the treatment study. EEG, electroencephalogram; SCR, skin conductance response; ENT, ear, nose, and throat; RI, residual inhibition.

treatment scheme). Both the change in the perception of the tinnitus and the perceived interference related to tinnitus, as well as success in the participants' ability to control residual inhibition would be used as outcome measures.

Before and after the training as well as at a 3-month follow-up, we also assess affective symptoms such as depression, anxiety, and psychological distress. Tinnitus-specific measures such as the Mini-Tinnitus Questionnaire (Hiller and Goebel, 2004), the Multidimensional Tinnitus Inventory (Flor and Schwartz, 2003) and the German version of the Tinnitus Handicap Inventory (Newman et al., 1996; German version: Greimel et al., 2000) will be used for assessment of the participant's benefit from the treatment. The habituation of the N_{100} of the event-related potentials as well as the skin conductance response to sounds before and after the training would also be assessed.

Participants for the study were recruited from cooperating institutions like the University Ear-, Nose-, and Throat-Hospital, Mannheim, via local press and by using the data pool provided by other ongoing studies at the institute. Exclusion criteria are: severe hearing loss, head or ear injury or surgical operations on the ear or brain, other outer or inner ear diseases, known physical cause of tinnitus, psychological disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association; German version: Sass et al., 1998), central acting medication, neuropathic pain, epilepsy, pregnancy, galactose intolerance, lapp lactase deficiency, glucose galactose malabsorption, and renal insufficiency.

The study was approved by the Ethics Committee at the Medical Faculty Mannheim of the University of Heidelberg according to the Revised Declaration of Helsinki, and informed consent was obtained from all participants.

Training

After obtaining a baseline of tinnitus severity and interference, and additional tests listed above, the participants started with training and substance intake. The treatment lasts 8 weeks. In week 1,

training is provided on 3 days at our institute. Each training session consists of the repeated presentation of an auditory stimulus that reliably elicits residual inhibition. For the training, the participants are instructed to deliberately prolong or deepen the residual inhibition state focusing on the auditory signal and subsequent imagery.

The participants are provided with visual feedback about their success in residual inhibition-control. For home training, participants received an audio CD including 30 min of residual inhibition training with the same stimulation parameters like the in-house training. Participants report the training success in their diary. To assess objective training success and for reasons of compliance, participants train at our institute once a week. Pregabalin or placebo is provided and side effects are monitored by the collaborating physician and recorded in the participant diary. Pregabalin is titrated from 75 to 150 mg and maintained at a daily dose of 150 mg. We use the minimally effective dose since we only use the drug for its adjunctive effects.

After the 8 weeks of treatment as well as at the 3-month follow-up, the psychoacoustic measures and the psycho-physiological measures are reassessed and the questionnaires are given. With the current study design we compare the additive effects of pregabalin vs. placebo with regard to the training. To distinguish between the effects of the pharmacological intervention and the training, we will follow up with a second study without training but only with the administration of pregabalin in one group and a placebo in another group. These data are currently being collected.

Conclusion

This study is part of a growing effort to develop mechanism-oriented treatments for tinnitus. Related approaches are attempts to influence tinnitus by transcranial magnetic stimulation (Langguth et al., 2005; Plewnia et al., 2007) or habituation training (Hazell, 1990). Future studies will show if tinnitus can be effectively abolished by these kinds of interventions.

Acknowledgments

This work was supported by the Tinnitus Research Initiative, Regensburg, Germany.

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CHAPTER 45

Auditory discrimination therapy (ADT) for tinnitus management

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Abstract: Auditory discrimination training (ADT) designs a procedure to increase cortical areas responding to trained frequencies (damaged cochlear areas with cortical misrepresentation) and to shrink the neighboring over-represented ones (tinnitus pitch). In a prospective descriptive study of 27 patients with high frequency tinnitus, the severity of the tinnitus was measured using a visual analog scale (VAS) and the tinnitus handicap inventory (THI). Patients performed a 10-min auditory discrimination task twice a day during one month. Discontinuous 4 kHz pure tones were mixed randomly with short broadband noise sounds through an MP3 system. After the treatment mean VAS scores were reduced from 5.2 to 4.5 ($p = 0.000$) and the THI decreased from 26.2% to 21.3% ($p = 0.000$). Forty percent of the patients had improvement in tinnitus perception (RESP). Comparing the ADT group with a control group showed statistically significant improvement of their tinnitus as assessed by RESP, VAS, and THI.

Keywords: cortical reorganization; tinnitus; auditory training; tinnitus management

Introduction

It is well known that the central nervous system (CNS) reorganize after peripheral deafferentation and tonotopic representation in the auditory cortex may change as a result of expression of neural plasticity (see Chapter 3).

Large cochlear lesions (i.e., complete deafness) can induce cortical reorganization, in a similar way as the deafferentation in total limb amputation (Flor et al., 1995, 2006) can cause re-organization of the somatosensory cortex. Even mild or moderate hearing impairment may initiate tonotopic changes in the cortex. Thus, studies in animals

have demonstrated that reorganization of the tonotopic map in the central structures of the auditory system can occur after high frequency hearing loss (Fig. 1) (Robertson and Irving, 1989; Rajan et al., 1993; Schwaber et al., 1993). Studies using recordings of magneto encephalographic (MEG) responses in individuals with high frequency hearing loss have indicated that the tonotopic frequency map of the contralateral auditory cortex expands adjacent to the frequencies of the hearing loss (Dietrich et al., 2001).

Behavioral evidence of lesion-edge over representation has also been proved (Mc Dermott et al., 1998; Eggermont and Komiya, 2000). Other evidence of reorganization of the auditory cortex in unilateral hearing loss patients comes from MEG studies in individuals with unilateral sudden

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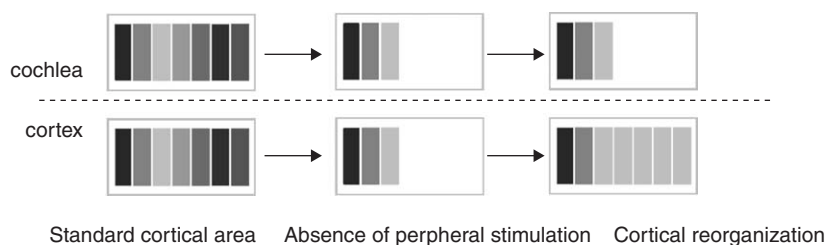


Fig. 1. Representation of cortical reorganization after cochlear damage on 4–8 kHz area. The cochlea has no possibility for reorganization while the auditory cortex increases the representation of the lesion-edge frequencies.

deafness. In such individuals, the responses from the ipsilateral hemisphere were abnormal (Vasama and Makela, 1995).

Mühlnickel suggested that specific acoustic stimulation of the damaged cochlear frequencies would enhance their cortical representation and reduce the over-represented edge regions, which had been related to tinnitus severity. Hence, tinnitus should be improved (Mühlnickel et al., 1998). In the somatosensory system, prevention of phantom limb pain and somatosensory cortex reorganization was achieved by sensory discrimination training (Flor et al., 2001). Flor et al. (2004) proposed that a specific training could be expected to cause expansion of the cortical regions responding to the trained frequencies and a shrinking of the representation of the neighboring cortical areas. Flor compared a group of 12 tinnitus patients trained with frequencies closed to the tinnitus pitch with another group trained with frequencies far away from the tinnitus pitch. Pairs of tones with frequencies close to or far from the pitch of the tinnitus (average 4672 Hz) were presented during 2 h daily, for 4 weeks. In 50% of the trials, there was a small frequency difference between the tones, in 50% of the trials, the tones were the identical. Difficulty was increased as learning progressed. The results did not show any significant difference in tinnitus improvement between the “close to” and “far from” groups. The group with more sessions of training (27–44) showed a significant reduction in tinnitus severity after 4 weeks, compared to the group with fewer sessions (13–23). The study failed to find a positive effect of training near to the tinnitus pitch compared to the absence of effect when training far from this

pitch. The design of our ADT protocols was based on the results by Flor. The participants did their training at home using an MP3 device. The duration of the sessions was of 10 min twice daily.

We present a prospective nonrandomized clinical assay of 46 patients referred to our tinnitus clinic from January 2005 to January 2006. Our goal has been to increase the cortical representation of 4 kHz and shrink the 6 and 8 kHz cortical areas.

Materials and methods

Patients were divided into two groups: a treatment group (27 patients) and a control group (26 patients). The control group was recruited from our waiting list (3–6 months to be attended in our tinnitus clinic). All patients gave informed consent to the study.

Age average of the treatment group was 49.5 ± 10.6 years old; the average age in the control group was 50.2 ± 9.3 . The left ear was more commonly affected than the right one (55% vs. 15%). Tinnitus was bilateral in 30% of the patients and it had been present for 42 ± 52 months (range 1 month–13 years).

All the participants in the treatment group and the control group had high frequency hearing loss (4–8 kHz threshold ≥ 25 dB, < 25 dB for lower frequencies). Average 4 kHz threshold was $44 \text{ dB} \pm 22$ and 8 kHz threshold was $53 \text{ dB} \pm 19$. Speech discrimination was not impaired in any of the participants. Acute and chronic noise-induced hearing loss was the most common diagnosis (30%).

Table 1. Psychoacoustic characteristics of the tinnitus from ADT-1 group ($n = 27$)

	ADT group	Control group
Loudness	10.9 dB \pm 7	11.4 dB \pm 9
Pitch	6000 Hz: 7 8000 Hz: 13	4000 Hz: 4 6000 Hz: 9 8000 Hz: 13
Minimal masking level (MML)	20 dB \pm 14	17 dB \pm 16
Residual inhibition	Total elimination: 8 Reduction in tinnitus loudness: 7 No changes: 5	9 10 6
Visual analog scale	5.2 \pm 1.9	5.35 \pm 1.4
Tinnitus handicap inventory	26.2% \pm 21.2	28.7% \pm 19.7

The control group consisted of patients from the waiting list. Their age, gender, and hearing loss were matched to that of the study group. In the control group left ear was more often affected than the right ear (45% vs. 20%). It was bilateral in 35% of them.

All the patients had a mild or moderate tinnitus handicap (THI < 56%). Table 1 shows the characteristics of the tinnitus in the treatment group and the control group. We have not included participants with severe tinnitus subjects in order to avoid other factors such as psychological disorders that could bias tinnitus response. Patients with anxiety or depression (according to STAI and BECK questionnaires) were excluded. The inclusion criterion for tinnitus pitch was patients whose tinnitus was matched at 6000 or 8000 Hz without any exception. All participants in the treatment group and the control group had a complete ENT examination. Their tinnitus was evaluated with regard to pitch, loudness, minimal masking level and residual inhibition. A visual analog scale (VAS) of intensity and a Spanish validation of the THI (Herraiz et al., 2001) were used for evaluation of tinnitus severity.

ADT treatment consisted of a 10-min auditory discrimination task, twice a day during 30 days using a domestic MP3 device. Every track had 400 units of 50 ms tones randomly mixed,

approximately, every 1.5 s. Eighty-five percent were broadband noise sounds and 15% were 4 kHz pure tones. There were five different tracks to be used according to the protocol (morning day one: track 1, evening day one: track 5, etc.). The patient marked every stimulus in a notebook. The effect of the treatment was assessed using the patient's response to the question "is your tinnitus better, same or worse since we started the treatment?" RESP, VAS, and THI. The SPSS 11.0 software program was used for statistical analysis of the results. Pearson's χ^2 and Fisher's exact tests were used for analysis of the difference between the treatment group and the control group. Pearson's correlation coefficients were used to estimate the mean reduction of tinnitus severity and handicap. All significance tests were two-tailed and conducted at the 5% significance level.

Results

Tinnitus improved in 40% of the participants (RESP). VAS mean score was reduced from 5.2 to 4.5 (statistically significant, $p = 0.000$) and THI decreased from 26.2% to 21.3% ($p = 0.000$) (two-tailed t -Student test). ADT efficacy did not depend on the etiology of the tinnitus. The characteristics of the tinnitus (loudness, minimal masking level, duration of the tinnitus, BECK depression questionnaire, VAS and THI scores) had no influence on results from the treatment (Fig. 2).

We found a statistical difference between ADT and WLG improvement considering the answer "my tinnitus is better" ($p = 0.006$, χ^2). VAS mean score after ADT showed a statistical significant improvement (reduction in 0.70 points, $p = 0.048$) compared to the control group (increase of 0.04 points). THI scores also decreased significantly (reduction in 4.9 in the ADT group compared to the increase of 1.46, in the control group, $p = 0.035$, Fig. 3).

Discussion

We have shown in this study that a specific protocol of ADT can improve tinnitus as demonstrated by VAS and THI. The protocol we used

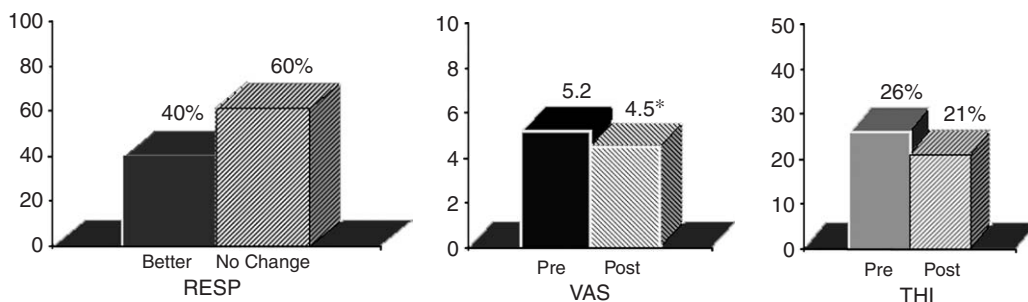


Fig. 2. Results of ADT-1 group after 1 month of auditory training. RESP: subjective response to the question “is your tinnitus better, same, or worse after the treatment?” VAS: Visual analog scale. THI: Tinnitus handicap inventory.

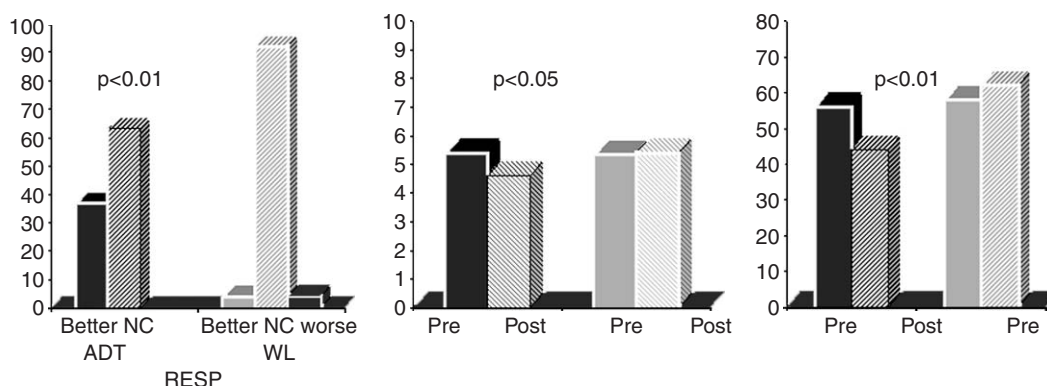


Fig. 3. Comparison between ADT-1 group and the Waiting List Group (WLG) for RESP, VAS, and THI.

Table 2. Description of ADT protocols used in our unit

ADT reference	Number of subjects	Description	Duration
ADT-1	29	85% white noise tones + 15% 4 kHz pure tones	10-min twice daily for 1 month
ADT-2	4	60% 8 kHz pure tones + 40% 4 kHz pure tones	10-min twice daily for 1 month
ADT-1-30m	6	85% white noise tones + 15% 4 kHz pure tones	30-min once daily for 1 month
ADT-Flor-4k	3	Pairs of tones (similar o deviant): 70% 4 kHz + 30% 4.5 kHz	10-min twice daily for 1 month
ADT-Flor-6k	2	Pairs of tones (similar o deviant): 70% 6 kHz + 30% 6.5 kHz	10-min twice daily for 1 month
ADT-Flor-8k	2	Pairs of tones (similar o deviant): 70% 8 kHz + 30% 8.5 kHz	10-min twice daily for 1 month

was based on studies by Mühlnickel et al. (1998) and Eggermont and Roberts (2004). According to the studies by Mühlnickel the frequencies close to but not similar to tinnitus pitch should be used in training while Eggermont's results indicates that frequencies close to that of the tinnitus pitch should be used in order to obtain optimal reorganization of the cerebral cortex. We do not know

if a different protocol would have yielded better results. It is possible that longer treatment time might have further improved the results, as might a larger number of sessions per day and longer duration of each session. In a pilot study we compared a 10-min twice daily with a 30-min once-daily protocol. Although we could not demonstrate a significant difference between the results,

there was a tendency to better results using 30-min training. Other ADT protocols designed and tested in our clinic are described in Table 2.

When evaluating the results of ADT treatment it should be considered that some of the observed effect could be a placebo effect or nonspecific factors such as focusing one's attention away from the tinnitus could have contributed to the improvement of the patients' tinnitus.

Abbreviations

ADT	auditory discrimination training
CNS	central nervous system
ENT	ear, nose, and throat
MEG	magneto encephalographic
RESP	tinnitus perception
THI	tinnitus handicap inventory
VAS	visual analog scale

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CHAPTER 46

Neurofeedback for treating tinnitus

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Abstract: Many individuals with tinnitus have abnormal oscillatory brain activity. Led by this finding, we have developed a way to normalize such pathological activity by neurofeedback techniques (Weisz et al. (2005). *PLoS Med.*, 2: e153). This is achieved mainly through enhancement of tau activity, i.e., oscillatory activity produced in perisylvian regions within the alpha frequency range (8–12 Hz) and concomitant reduction in delta power range (0.5–4 Hz). This activity is recorded from electrodes placed on the frontal scalp. We have found that modification of the tau-to-delta ratio significantly reduces tinnitus intensity. Participants who successfully modified their oscillatory pattern profited from the treatment to the extent that the tinnitus sensation became completely abolished. Overall, this neurofeedback training was significantly superior in reducing tinnitus-related distress than frequency discrimination training.

Keywords: neurofeedback; EEG; tinnitus

Tinnitus in relation to abnormal oscillatory brain activity?

Subjective tinnitus, an auditory sensation that appears without the presence of an external physical source of the sound is a symptom rather than a nosological entity. Treatments of this condition have included cognitive-behavioral therapy (Andersson, 2002), psychotherapy (Goebel, 2001), “tinnitus retraining therapy” (Jastreboff and Jastreboff, 2006), biofeedback (Landis and Landis, 1992), physical therapy (Rief et al., 2005), transcranial magnetic stimulation (Langguth et al., 2006), auditory frequency training (Flor et al., 2004), prolonged rest and relaxation (Weber

et al., 2002), and the administration of such agents as lidocaine (Kalciglu et al., 2005). Despite isolated reports of success, no treatment has been found to be effective in general (Dobie, 1999).

Several central nervous phenomena have been proposed to explain the emergence of tinnitus. However different, all assume a decisive role of reduced afferent input to central auditory regions usually due to damaged hair cells of the cochlea. One proposed mechanism draws analogies to somatosensory phantom pain, where somatotopic maps reorganize as a result of altered afferent input (Elbert and Heim, 2001). Reduced sensory input to central neurons may change their receptive fields and make them become sensitive to input from neighboring regions through expression of neural plasticity (see Chapter 3). In the auditory system this may lead to an overrepresentation of audiometric edge frequency regions, and that may

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cause the phantom sensation of tinnitus. In the somatosensory system such map reorganization, has been shown to be linearly correlated with the amount of phantom limb pain (Flor et al., 1995) (Chapter 4). Reorganization of the auditory cortex occurs after hearing loss as shown in many studies in animals (Eggermont and Roberts, 2004). One magnetoencephalographic (MEG) study in humans with tinnitus has shown distortions of the tonotopic map in auditory cortex that was related to the tinnitus sensation (Muhlnickel et al., 1998).

Training that aims at reestablishing afferent input would be expected to reverse maladaptive reorganization. Clinical studies have used frequency discrimination trainings (FDTs) targeted at the region around the tinnitus frequency (Flor et al., 2004), or within the deafferented frequency region (see Fig. 4, p. 494), but without noticeable benefit regarding tinnitus. Nevertheless, these negative clinical findings need not necessarily contradict that map reorganization may be sufficient to produce tinnitus (Weisz et al., 2006) (Chapter 6). Hair-cell damage that alters the cochlear frequency processing may have interfered with the attempts to direct afferent input to specific neuronal assemblies.

Deprivation of input to the auditory system may alter spontaneous activity in groups of neurons. Given that tinnitus is a continuous sensation, there should be an ongoing neural signal that codes the perpetual sensation. The question one must ask is how does intrinsic activity elicit a sensation? Different assumptions from animal research have been made regarding the relation between altered neural activity and tinnitus. It has been hypothesized that tinnitus may be caused by increase of firing rates or altered synchrony of firing (Eggermont and Roberts, 2004). Since the onset of tinnitus usually follows noise trauma, which also alters neural synchrony (Norena and Eggermont, 2003), these two phenomena may be related. In individuals with tinnitus, we found an abnormal ongoing spontaneous pattern of magnetic brain activity (Weisz et al., 2005). Both MEG and electroencephalography (EEG) represent the summed activity of many neurons and reflect synchronous activity in entire neuronal populations. In

individuals with tinnitus abnormalities in the MEG are pronounced in recordings from temporal regions where slow waves in the delta range (0.5–4 Hz) are increased, and the alpha activity (8–12 Hz) is reduced. The abnormalities were strongly correlated with the level of tinnitus-related distress (see Fig. 1).

Similar patterns were observed in other disorders, and Llinas et al. (2005) hypothesized that deprivation of input in general (in this case hearing loss), leads to hyperpolarized thalamic neurons, which in turn trigger bursting activity at ~4 Hz (Jeanmonod et al., 1996). The bursting activity spreads across large parts of the cortex and can be detected on a macroscopic level as changes in recorded MEG or EEG. The slow-wave activity in MEG or EEG recordings could also be the result of hypoactivation of cortical neurons. The described bottom-up process could also activate top-down pathways by input from cortico-limbic pathways, which modulate emotional and motivational processing. Slow oscillatory activity could be the neural signature of the coupling between anatomically distant brain regions, as occurs in normal information processing (Sauseng et al., 2005). However, enhanced slow oscillatory activity was not the only observed abnormality in the MEG of individuals with tinnitus; reduction of alpha power around 10 Hz in recordings from temporal regions (so-called *tau* rhythms) is hypothesized to be a normal reaction to sound (Hari and Salmelin, 1997; Lehtela et al., 1997). As individuals with tinnitus continuously hear an internal sound, it is conceivable that the power of their *tau* rhythms is reduced. Weisz et al. 2007 (Chapter 6) provide more information regarding the relationship between ongoing oscillatory activity and tinnitus.

Slow wave EEG activity, especially that occurring during sleep, has been associated with brain silence and the decrease of thalamic input to the cortex (Steriade and Timofeev, 2003). In the waking state, slow waves in the EEG occur in many developmental and degenerative disorders, in toxic and metabolic encephalopathy, and in other neurological conditions. The anatomical location of focal neural generators of slow waves is usually in the vicinity of structural lesions such as cerebral

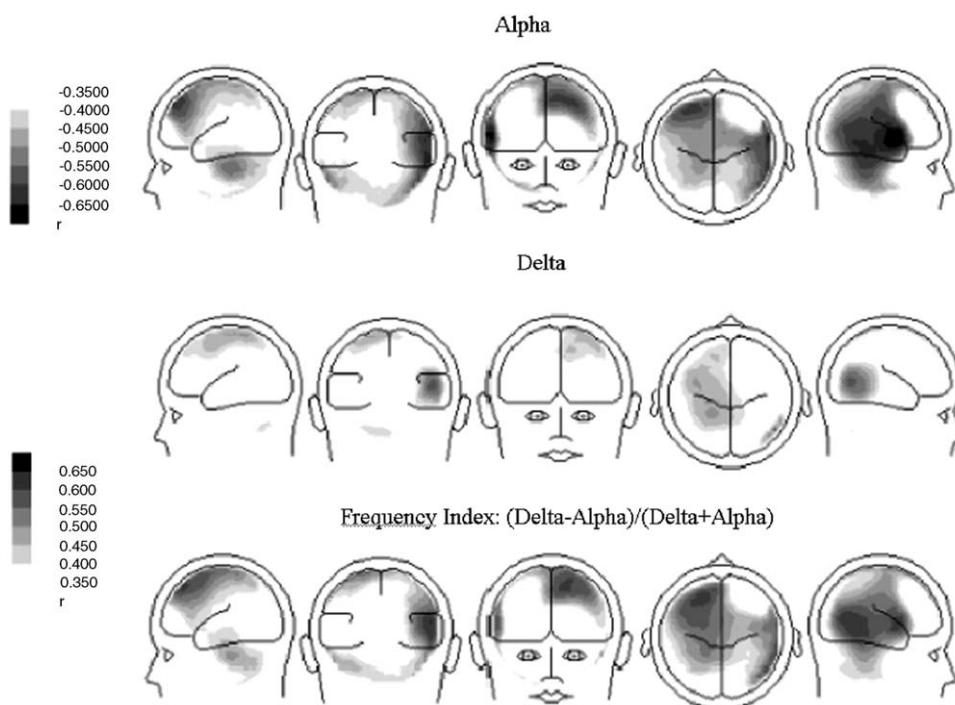


Fig. 1. Distribution of correlation coefficients between the tinnitus-related distress (score on the Tinnitus Questionnaire) and the power in alpha, delta, and a frequency index of both bands, respectively. Effects are largest for right temporal and left frontal sources. (Adapted with permission from Weisz et al., 2005.)

infarcts, contusions, local inflammations, tumors, and subdural hematoma (Walter, 1936; Tanaka et al., 1998; de Jongh et al., 2003). The output of these generators varies with the level of metabolism and blood flow and depends on the magnitude of the insult (Strik et al., 2002; Hensel et al., 2004).

We consequently propose that neural networks in at least three regions are involved in tinnitus, namely: temporal areas, which are relevant for the processing of perceptual features of tinnitus, and frontal and limbic regions, which are involved in processing the emotional and motivational features (i.e., the perceived distress) of the phantom sound. Slow oscillatory activity couple the involved regions together. The normal auditory alpha/tau rhythms are reduced due to a permanent processing of this internal sound (tinnitus). If these elements were of fundamental importance in the generation of tinnitus, normalization of the aberrant rhythms would be expected to alleviate tinnitus. In the present study, we have explored the

possibility to modify this abnormal activity through the technique of neurofeedback, i.e., by recording the EEG signal, extracting relevant parameters, and displaying this information to the person with tinnitus.

Neurofeedback: background and previous application

In individuals with chronic tinnitus the aim was to modify the aberrant rhythms in the EEG — mainly the enhanced delta and reduced tau power. The technique is described in detail elsewhere (Dohrmann et al., submitted). If the abnormal brain rhythms were causally related to the tinnitus, it would be expected that changing the spontaneous activity pattern would modify the tinnitus and its associated distress.

Neurofeedback has proven to be effective in modifying the characteristics of spontaneous and

evoked brain activity (see review by [Rockstroh et al., 1984](#)). By means of an EEG-based training method, individuals can learn to self-regulate distinct features of their ongoing brain activity, such as the power in a certain frequency band.

The principles of neurofeedback are: the EEG signal is recorded, processed, and converted into a contingent auditory and/or visual feedback signal for the patient. Training for the task of neurofeedback aims at teaching the patient an association between the signal and the most recent mental state. *Instantaneous* feedback to the patient is crucial for training. If the patient is successful in changing the EEG and the brain activity reaches a certain pre-defined level, the patient receives a reward, such as a smile or applause.

Research using neurofeedback began in the late 1960s with work on uncontrolled epilepsy as well as training in alpha feedback for relaxation ([Nowlis and Kamiya, 1970](#); [Travis et al., 1974](#)). Today, it is applied to the field of epilepsy ([Elbert et al., 1991](#); [Rockstroh et al., 1993](#)) and attention deficit/hyperactivity disorders (AD/HD) (e.g., [Monastra et al., 2000](#); see also [Rockstroh et al., 1990](#)). Although the investigation of neurofeedback in treatment of AD/HD stands in the forefront, there is a lack of standardized parameters of implementation (such as number of sessions, controlled clinical trials, parameters of success, registration of the EEG activity; see [Duffy, 2000](#); [Ramirez et al., 2001](#)).

Studies exploring the effect of neurofeedback on tinnitus are scarce. Two studies ([Gosepath et al., 2001](#); [Schenk et al., 2005](#)) have supported the assumption that distress in general is associated with a reduction in the power in the alpha band recorded from the posterior scalp and enhancement of the power in the beta (14–30 Hz) band. On the basis of these findings it has been hypothesized that the vicious circle of strain, anxiety, and depression that is initiated in tinnitus can be interrupted through relaxation and by upregulating the alpha activity (sign of increased relaxation) and downregulating the beta activity (sign of decreased stress).

The approach described in this chapter differs essentially in that the activity being modified is different in terms of its anatomical localization

and its presumed type of generators ([Dohrmann et al., submitted](#)). While posterior sites have been the regions of interest in many studies, we focus on temporal and frontal regions, which we believe are mainly involved in the psychoacoustic and distress aspects of chronic tinnitus. We therefore record EEG from F3, F4, Fc1, and Fc2 positions on the scalp. First, the tau activity is in the frequency range of alpha activity but is presumed to be generated in sylvian regions of the brain, including the auditory cortex, from where it projects to frontal regions. Secondly, the slow-wave activity would be an indication of deafferented tinnitus-related neuronal networks and not only a sign of general distress. More specifically, the deafferented thalamus might degenerate causing the respective cortical drive to cease.

While it seems logical to assume that distress from tinnitus is related to its loudness it is also conceivable that a relief of distress results in a reduction of the tinnitus intensity. Nevertheless, it has been reported that loudness and distress are relatively marginally connected ([Henry and Meikle, 2000](#)). These conclusions could, however, depend on the procedures used to treat tinnitus. Most therapies focus on coping with the annoyance of the tinnitus and less on reduction or abolishment of the tinnitus itself ([Andersson and Lyttkens, 1999](#)). The advantage of neurofeedback over input-based (sound) therapies such as FDT, which are based on assumptions of central nervous reorganization, is that the treatment using neurofeedback is not affected by hearing loss.

Effects of a specific tau/delta neurofeedback training

Based on the hypotheses outlined above, we compared the effectiveness of different neurofeedback protocols in reducing the tinnitus in 21 individuals with chronic tinnitus (9 females and 12 males, age 31–62, median 48 years). The mean duration of their tinnitus was 8.7 years ($SD \pm 7.4$), the mean tinnitus intensity of 25 dB HL ($SD \pm 11.7$), and a mean distress level of 26.5 points (slight distress; $SD \pm 15.3$) on the Tinnitus Questionnaire ([Goebel](#)

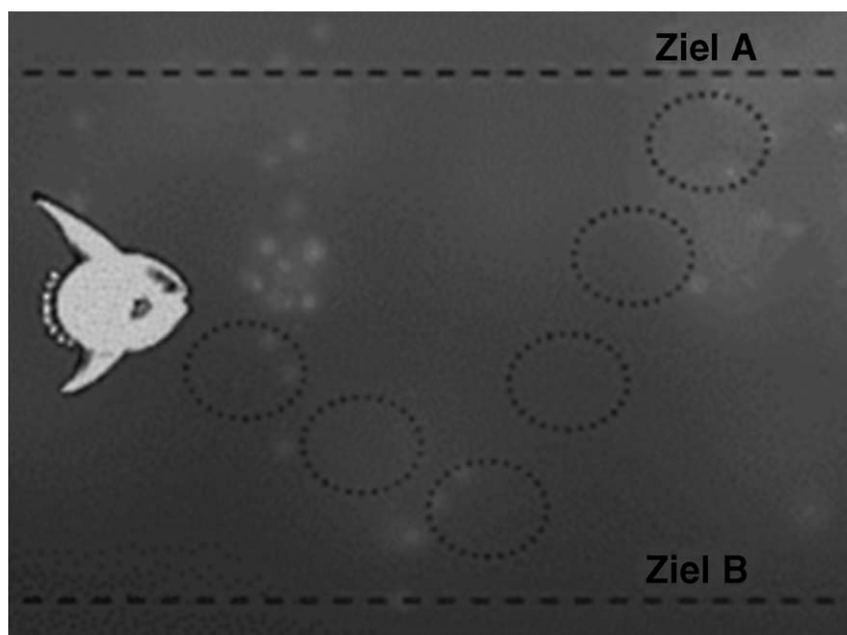


Fig. 2. The schematic fish on the patient monitor that was to be “moved” up or down (depending on the feedback protocol) during neurofeedback training. The height of the fish represented the amplitude/power of the specific frequency band. (By courtesy of Eldith© Corporation, Germany.) (See Color Plate 46.2 in color plate section.)

and Hiller, 1998), distress scale from 0 (no distress) to 84 points (very severe distress).

The participants in the study underwent a training program comprising 10 sessions (net training time per session: 30 min) over the course of 4 weeks. EEG was recorded from electrodes placed at fronto-central positions (F3, F4, Fc1, and Fc2). Eleven participants aimed at enhancing the ratio of tau-to-delta power (TDR), five participants aimed at enhancing tau power (without feedback about delta power), and five participants aimed at reducing delta power (without feedback about tau power).

Feedback was provided through the use of a symbol (e.g., a fish; see Fig. 2) that moved from left to right on a computer screen. A rise of the symbol indicated successful enhancement of the TDR and the tau power, respectively. In the delta protocol group, a drop in the symbol indicated successful decrease of delta power. A sunshine symbol indicated that the participant had reached an individually adjusted threshold. Participants

were given no particular instructions on how to obtain the anticipated change in the EEG activity but they should change their mental activity to get the symbols on the screen to move in the anticipated way. We also asked them not to engage in any muscular activity, including eye movements and blinks that they might think would facilitate the changes in their EEG activity as indicated by the movement of the figures on the screen.

We monitored training success by matching the intensity of the tinnitus to a 1 kHz test tone (psychoacoustic measure using the audiometer) as well as by measuring the power in the appropriate frequency bands of the resting EEG each before and after the training. It must be emphasized that the participants in the study were unaware of the intensity values they matched to their tinnitus. Various measures of distress related to tinnitus were surveyed once a week using a German Tinnitus Questionnaire (Goebel and Hiller, 1998). Tinnitus status was also measured at a 6-week and 6-month follow-up post-training.

EEG normalization

For every pre and post session we calculated the tau-to-delta power ratio and the results showed a significant enhancement of this TDR with an effect size of 0.67. Overall, participants showed an improvement of 71% (ranging from 32% to 325%). As shown in Fig. 3, participants improved with regard to normalization of their TDR *within* a session (after training the EEG power is above its values before the training). This normalization develops gradually *between* sessions, confirmed by an ascending linear trend for pre ($p = 0.016$) and post ($p = 0.007$) TDR-values.

The achieved normalization of the EEG did not differ significantly among groups with different feedback protocols ($p = 0.8$, repeated measures ANOVA with between-subject factor “group” comprising the three levels: tau, delta, and tau/delta) (Table 1).

Many of the participants who were extraordinarily successful in controlling their brain oscillation reported that they would start a session by putting themselves in a mental state of relaxation using approaches they had learned in courses on autogenic training or that they developed

personally. One participant who achieved complete relief from tinnitus at the end of treatment had imagined good experiences of job-related success.

Reduction of tinnitus

Starting with a tinnitus intensity of 25 dB HL on average ($SD \pm 11.7$), participants reduced the intensity of their tinnitus to a mean of 16 dB HL ($SD \pm 13.3$) after the training period and then maintained the intensity level below baseline for 6 weeks and 6 months later (20 ± 13.7 dB and 17.4 ± 11.9 dB, respectively). During training, the intensity of the tinnitus did not decrease as

Table 1. Allocation of the three different neurofeedback protocols

Group	Group size	Feedback measure	Treatment goal
1	5	Tau (8–12 Hz)	Enhancement of tau
2	5	Delta (1–4 Hz)	Reduction of delta
3	11	Tau/delta-ratio	Enhancement of the tau/delta-ratio

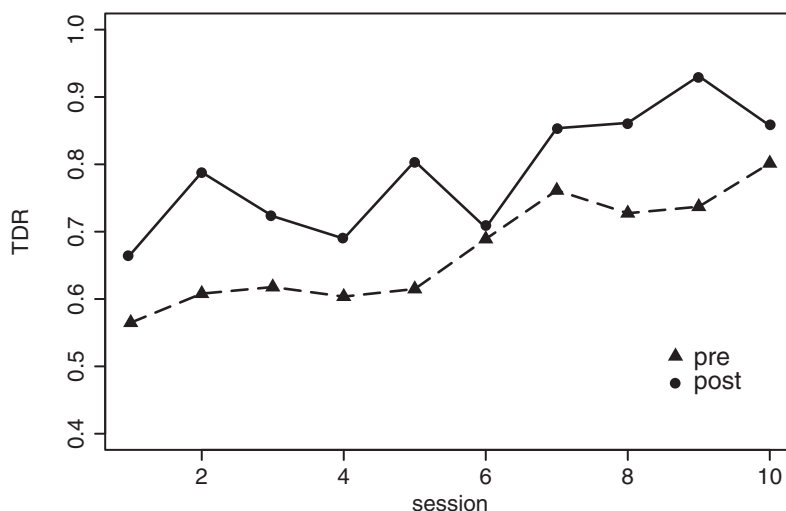


Fig. 3. Development of the mean tau/delta values in the 5 min resting EEG before (dashed line and triangles) and after (filled circles and solid lines) the neurofeedback session. The values are calculated over the whole training group ($n = 21$), independent of the three feedback protocols. It is evident that the post-tau/delta ratio of every session lies above the pre-ratio (*within* learning effect; even the differences are not significant, tested with t -test). Moreover, there is an improvement *between* the sessions, showing a gradually ascending linear trend.

gradually as the EEG power ratio, but did so substantially in the first five sessions, and to a lesser extent in the second half of the training. Again, there is no significant difference between the reductions of the three protocol groups.

The individuals who participated in the training reduced their tinnitus-related distress from a mean of 27 ($SD \pm 15.3$) points on the Tinnitus Questionnaire before training to a mean of 19 points ($SD \pm 15.3$) after the tenth session. In the follow-up measures participants showed a mean of 20 points ($SD \pm 18.0$) after 6 weeks and a mean of 20.5 points ($SD \pm 20.2$) after 6 months. It should be noted that changes from the very low baseline level are indeed noteworthy given that many clinical studies only investigate participants presenting with high levels of distress.

Frequency discrimination training

The outcome of the pooled neurofeedback groups ($N = 21$) was compared to a group ($N = 27$) who

received auditory FDT targeted to achieve map normalization, i.e., a reduction of the hearing-loss induced reorganization of neural structures. The use of FDT was inspired by the finding of map reorganization in some individuals with tinnitus (Muhlnickel et al., 1998).

There were 27 participants, 23 men and 4 women, in the FDT group; their age ranged from 24 to 65 years with a median age of 55. The mean duration of their tinnitus was 9.1 years ($SD \pm 7.58$, range of 1–32 years).

Both the neurofeedback and the FDT group received 10 training sessions and 1 pre-training session in which they received information about the procedures they were to undergo. The level of distress at baseline is similar for the two groups (neurofeedback: mean of 27 ($SD \pm 15.3$) points; FDT: mean of 34.5 ($SD \pm 16.4$) at first baseline and 29.5 ($SD \pm 16.8$) directly before training start).

Participants in the neurofeedback group had a significant decrease in the distress scores (Fig. 4) while the distress experienced by the participants in the FDT was not significantly affected by the

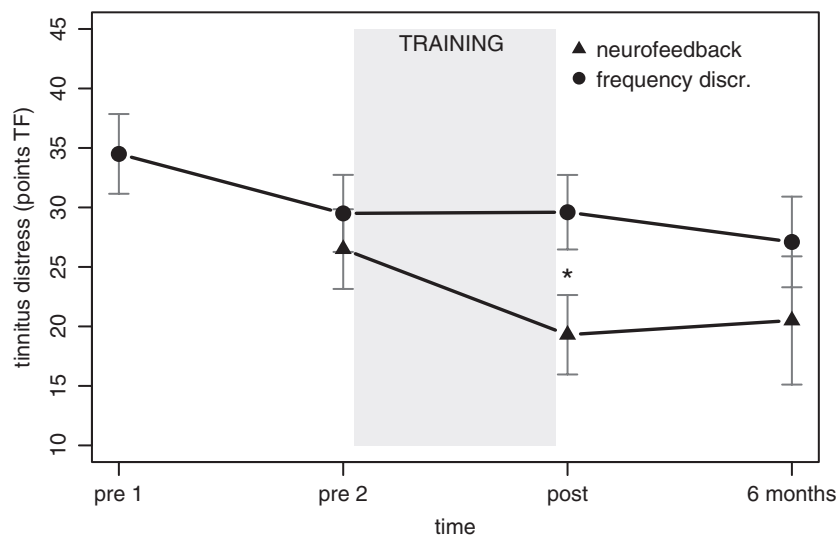


Fig. 4. Mean distress values (± 1 standard error) for the frequency discrimination group (triangles) at the initial interview (pre 1), 1 week before training onset (pre 2), immediately following the training period (post), and 6 months follow-up, and the neurofeedback group (circles) before training (pre 2), after (post), and 6 months later (follow-up); values for “pre 1” are nonexistent. The gray bar displays the training period. The asterisk indicates a significant difference between the groups *after* the training period, whereas there is no significant difference at pre 2 and 6 months follow-up between the two training groups. Tinnitus distress was measured with the German Tinnitus Questionnaire (TF) and comprises values from 0 to 84 points, with high values indicating severe distress. Both samples have slight to moderate initial distress values (0–46).

training. Expectancy of treatment produced a reduction from 34.5 to 29.5 points on the Tinnitus Questionnaire before the actual start of the training (pre 1 to pre 2), but no further reduction in distress then occurred due to the training. The finding that the FDT had little success in alleviating distress in tinnitus is in agreement with the results of other studies (Flor et al., 2004).

Relation between EEG normalization and tinnitus relief

The participants who successfully modified their oscillatory brain activity had the greatest reduction in their tinnitus (Fig. 5) with a correlation $r = -0.74$ ($t(18) = -4.69$, $p < 0.001$). The correlations of change in the tau activity with the intensity of the tinnitus ($r = -0.29$), and change in delta

activity with tinnitus intensity ($r = 0.37$), were not statistically significant ($p > 0.05$). Concerning the distress, there is neither a significant correlation between the change of TDR and distress change ($r = 0.22$, n.s.), nor between each single frequency band with the distress change.

Changes in the TDR may reflect changes in tau, delta, or both. To determine the relevant predictive parameter(s), participants were classified in four groups based on their ability to modify tau and delta irrespective of the feedback protocol. Participants who modified *both bands* simultaneously had the strongest tinnitus relief and some even experienced complete relief from their tinnitus. The average reduction in tinnitus intensity was 71%, which was significantly greater than achieved by the other three groups (Fig. 6; comparison with the “no change” group: $t = 2.72$, $p = 0.017$). Participants who only changed one band did not reduce their tinnitus significantly (tau: 26%;

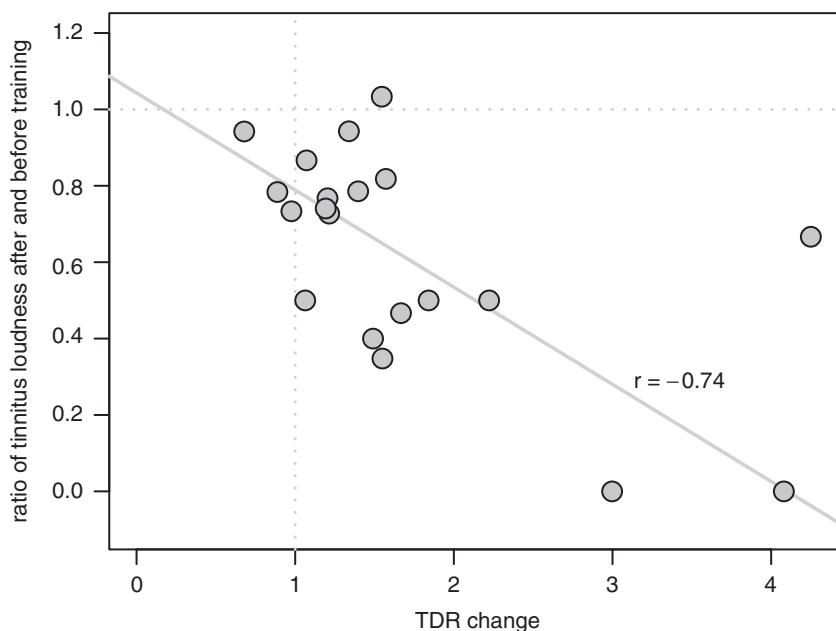


Fig. 5. Correlation between the change in tau/delta power (x-axis; displayed as the tau/delta ratio after the training divided by the tau/delta ratio before the training) and the change in tinnitus intensity (y-axis; ratio between the intensity after the therapy and the intensity before the therapy). Values in tau/delta change above 1 (dashed line) indicate a high normalization (= enhancement of tau and/or reduction of delta), whereas slight values in tinnitus intensity reduction (under the dashed line) indicate large reduction. Two patients with large normalization show a tinnitus change of zero, indicating no tinnitus at post-training. The added line is the regression line with the regressor of tinnitus reduction and the predictor of tau/delta change. These analyses are independent from the different feedback protocols.

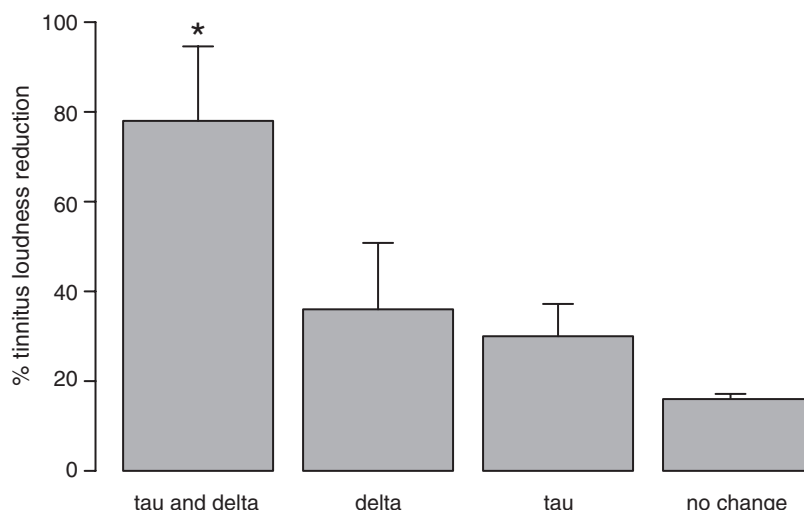


Fig. 6. Barplot of tinnitus intensity reduction depending on which frequency band could be modulated. This analysis is independent of the three different feedback protocols. The whole training group is divided into four clusters depending on the value of tau change pre-post training and delta change pre-post training being above or under the median of changes. The left cluster comprises patients with values *above* the median of tau change and simultaneously *under* the median of delta change. These patients are referred to as the most successful ones as they were able to alter both bands in the desired direction. At the same time, they had the greatest tinnitus intensity reduction. The reduction is significantly higher than in subjects managing to alter delta (but not tau, second cluster from the left), or in the ones managing to change tau (but not delta, third cluster), and finally those subjects who neither enhanced tau nor reduced delta (fourth cluster). The reduction in the fourth cluster is ~16%, indicating a placebo effect.

delta: 36% reduction) compared to the patients who showed no change at all. The “no change” group also reduced their tinnitus intensity by 24%, although these participants were not able to normalize tau or (nor?) delta, thereby representing an estimate of the placebo effects of treatment.

Neurofeedback in the future: notions and suggestions for improvement

The results described above indicate that neurofeedback may be an effective tool for treatment of chronic tinnitus patients. The neurofeedback protocol described above consisted of 10 training sessions dispersed across 4 weeks. Compared to other studies, this was a relatively small number of treatment days. Gosepath et al. (2001) treated their tinnitus participants for 12 days, Schenk et al. (2005) for 15 days. We conducted a pilot study with twice as many sessions (20 treatment days) over 4 weeks and TDR-feedback as usual. All

four participants were able to normalize their power-spectrum during the entire therapy. A strong initial improvement was followed by a flattening of the learning curve during sessions 11–20 suggesting that longer trainings may bear additional but small benefits. The intensity of the training was greater in this group than the study described above with five trainings a week for four consecutive weeks. The competencies that patients learn during the therapy must be continued in their everyday life. We recommend that the use of neurofeedback therapy for chronic tinnitus include more than 10 sessions, ~3 days per week. Since the abnormal oscillations in chronic tinnitus sufferers have been occurring for several years, it requires a significant amount of exercise to return them to normal functioning.

Instruction

The results of the aforementioned neurofeedback study suggest that success (i.e., alleviation of

tinnitus) depends on how much the individuals are able to normalize their brain rhythms (see Fig. 5). Participants who were not able to control their TDRs did not benefit from the training. This means that if this method is used in treatment of patients with teaching of the patients regarding how to gain control over their brain activity would likely improve the results of this method.

The original basis for neurofeedback is learning through operant conditioning (Travis et al., 1974; Rockstroh et al., 1984). Alternatively, in a study of neurofeedback the signal alone may be sufficient for training the participant. The feedback provided may raise awareness in the participant enough that self-regulation of brain activity can occur (Rockstroh et al., 1984). Therefore, participants do not learn from the therapist; rather they are provided feedback when a particular emotional or mental state is achieved and they learn through this feedback. The optimal conditions for improvement may indeed be a combination of a therapist or instructor teaching participants a behavior that can lead to normalization of brain rhythms and provide the participant with feedback. Currently, the workgroup of Del Bo (Milano, Italy) is investigating the effect of a combined tau/delta neurofeedback training, as proposed here, along with the Tinnitus Retraining Therapy (Jastreboff, 2006).

Feedback protocol and electrode set-up

We used three different feedback protocols in the study described above (TDR, tau alone, and delta alone). Regardless of the protocol those participants who were able to change the TDR in the desired direction benefited most from the training (see Fig. 6).

On the basis of these results, we concluded that the tau- and delta activity are not independent of each other but are systematically connected. This should be considered when this method is adapted for clinical use in treating patients with tinnitus. The ratio between the powers in these two EEG

bands is not an optimal measure of success in changing the oscillations in the EEG for tinnitus suppression because changes in one band are enough to produce success in the training. We therefore currently investigate the effects of a protocol that enables us to provide specific feedback of the tau- and the delta band simultaneously. For that purpose we display delta power on the abscissa and tau power on the ordinate of the computer display used by the person who is undergoing treatment. A feedback symbol moves across the monitor in two-dimensional space. The person's task is to bring the symbol into the quadrant that represents an enhancement of tau- and a reduction of delta activity and make it stay there.

There are many possibilities as to where to place the electrodes for recording the EEG signal that is used for the training. In the present study we used four electrodes placed at C3, C4, Fc1, and Fc2. This setup was chosen because fronto-central electrodes are likely to pick up activity from the auditory cortex, which are largely tangentially oriented. However, the measured activity also represented frontal regions. To see whether training success is related to changes in temporal or in frontal sources and to investigate their relationship to the alleviation of tinnitus symptoms, whole-head EEG-data might be helpful and are also currently implemented in our ongoing neurofeedback study.

Prediction of training success

It would be beneficial to be able to predict how successful the training of a specific person would be and that would make it possible to identify patients who would benefit most from this form of neurofeedback therapy. For that purpose we performed a post-hoc regression analysis with the pre/post-reduction of tinnitus loudness as the dependent variable and with the following regressors: pre tau power, pre delta power, pre/post-change of the TDR, pre tinnitus loudness (dB), pre tinnitus severity (measured with the "Tinnitus Questionnaire"), duration of tinnitus, age, sex,

and side of tinnitus perception. The power of tau and delta before therapy, as well as the normalization of both frequency bands (TDR pre/post), were the only significant predictors for the reduction of tinnitus loudness. The model indicates that parameters of the individual tinnitus perception such as the duration of tinnitus, side of perception, severity and loudness of tinnitus, or subject-specific factors such as age and sex, do not influence the outcome of the therapy. It is rather the pattern of oscillatory activity before and the amount of normalization during the therapy that determines the success in reducing the loudness of tinnitus. The prediction of the model was highly significant ($p = 0.001$, $F_{9,10} = 10.1$) and explained 81% of the variance in tinnitus loudness reduction (adjusted R^2 of 0.811).

In addition, we found the duration of tinnitus to be negatively related to the success of the treatment ($r = -.41$, $p = 0.08$). Thus, patients with a short history of tinnitus profit most from the neurofeedback training. Given the assumption that there is a network of ongoing pathological neural oscillations producing tinnitus, this observation seems plausible. As a result, the longer the history of tinnitus, the longer the history of abnormal oscillations. These oscillations may then form a stabilized neural network over time. If a patient begins neurofeedback training shortly after the onset of tinnitus onset, the connections of the tinnitus network may not yet be consolidated and are thus more likely to revert back to a more regular activity level.

Summary

The use of neurofeedback in the treatment of chronic tinnitus is an emerging field of research. Our approach is based on the modulation of specific abnormal oscillations. We focus on the normalization of the tau-to-delta power ratio, generated in temporal and possibly frontal areas. The greatest reduction in the loudness of tinnitus occurred in participants who were capable of normalizing the TDR. Participants in this study benefited more than participants in a study using

auditory discrimination training to reduce tinnitus. Modulation of specific abnormal brain oscillations via neurofeedback seems to be a potential route for alleviating the intensity and related psychological distress of chronic tinnitus.

Abbreviations

AD/HD	attention deficit/hyperactivity disorders
EEG	electroencephalography
FDT	frequency discrimination training
MEG	magnetoencephalography
TDR	tau-to-delta ratio

Acknowledgments

Our research is funded by the Deutsche Forschungsgemeinschaft and the Tinnitus Research Initiative. We would like to thank Isabel Lorenz, Anke Trefz, Susanne Völk, and Sylvia Datson for support during data collection.

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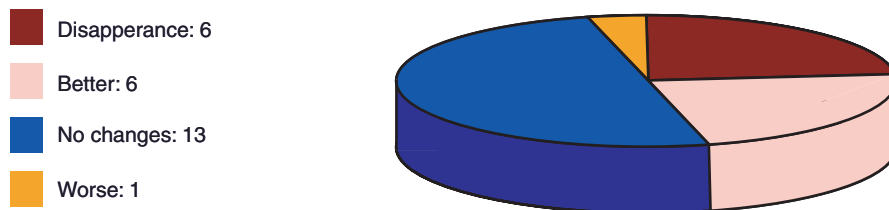


Plate 37.2. Response to TENS treatment after 2 weeks. Tinnitus improvement was referred by 46% of the patients (disappearance + better). (For B/W version, see page 392 in the volume.)

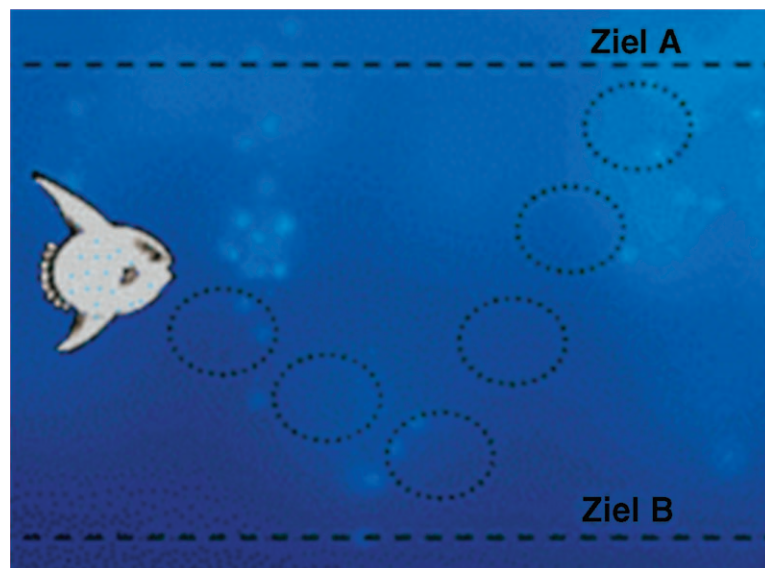


Plate 46.2. The schematic fish on the patient monitor that was to be “moved” up or down (depending on the feedback protocol) during neurofeedback training. The height of the fish represented the amplitude/power of the specific frequency band. (By courtesy of Eldith© Corporation, Germany.) (For B/W version, see page 477 in the volume.)

CHAPTER 47

Residual inhibition

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Abstract: Following offset of an appropriate masking stimulus, tinnitus may remain suppressed for a period, typically less than a minute. This phenomenon is known as “residual inhibition” (RI). This chapter reviews the psychoacoustic properties of RI and their relation to hearing impairment, tinnitus spectra, and the spectra of masking stimuli. RI is also contrasted with tinnitus suppression produced by repetitive transcranial magnetic stimulation (rTMS) the cortical effects of which do not require the ear to reach the brain. Although the two procedures act in different ways, both may reduce tinnitus by interrupting abnormal synchronous activity among networks of neurons that generate tinnitus. Therapies that induce tinnitus suppression by these methods have been reported to reduce tinnitus distress by processes that are not well understood.

Keywords: tinnitus; residual inhibition; masking; transcranial magnetic stimulation; neural synchrony

Introduction

One of the fundamental properties of tinnitus is that it can be masked by external sounds. In his classic studies of tinnitus masking, Feldman (1971) observed that a substantial number of participants experienced a brief reduction in their tinnitus following the cessation of the masker. This phenomenon has come to be known as “residual inhibition” (RI), although the term “residual suppression” is more neutral with regard to its possible underlying mechanisms (Terry et al., 1983). Because RI is one of the few procedures that may reduce or eliminate tinnitus for brief periods, it is surprising that except for foundation studies now more than 20-years-old, few studies on RI have been published (Henry and Meikle, 2000). It is possible (although by no means certain) that the

mechanisms that are involved in RI are similar to (or overlap with) those that cause the generation of tinnitus. If this working hypothesis is accepted, efforts to understand RI should take guidance from advances in our knowledge of the mechanisms underlying tinnitus.

In this chapter I review early and recent research on the psychoacoustic properties of RI and their relationship to properties of tinnitus. An attempt is made to understand these phenomena in terms of common underlying neurophysiological mechanisms. Evidence from many different studies (Chapter 2) suggests that most forms of tinnitus result from a loss of inhibition in central auditory structures consequent on hearing impairment or the aging process. When inhibitory deficits occur, synchronous neural activity that is normally constrained by feedforward inhibition to acoustic features in the stimulus (normal auditory perception) may develop spontaneously among networks of neurons in the affected auditory

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cortical regions, giving rise to the sensation of tinnitus (Eggermont and Roberts, 2004; Weisz et al., 2007) (see Chapters 2 and 6). Synchronous activity in the auditory cortex appears to recruit via intracortical or corticothalamic pathways a distributed network involving other brain regions (Schlee et al., 2007), some of which have been identified by anatomical (Muhlau et al., 2006) and functional brain imaging studies (Melcher et al., 2000; Lockwood et al., 2001; Wienbruch et al., 2006; Plewnia et al., 2007). This general view of the pathophysiology of tinnitus has implications for the psychoacoustic properties of tinnitus, for tinnitus masking, and for understanding RI, which are discussed in this chapter. Tinnitus suppression induced by repetitive transcranial magnetic stimulation (rTMS) (Chapters 34 and 35) is also mentioned, because it may achieve some of its effects by processes overlapping those of RI. Study of the clinical benefits of RI and from treatment with rTMS is an emerging area of investigation (Vernon and Meikle, 2003; (see Chapter 49).

Psychoacoustic properties of tinnitus, masking, and RI

Feldman categorized masking effects into three main categories according to whether auditory thresholds and tinnitus masking curves converged only at some frequencies (“convergence,” 34% of patients with chronic tinnitus), at most frequencies (“congruence” type, 32% of patients), or showed only a weak trend (“distance” type, 22% of patients). The existence of these patterns was confirmed by subsequent studies using pure tones or narrow band noise as masking stimuli (Mitchell, 1983; Tyler and Conrad-Ames, 1984), with convergence tending to be the most common form (53% in the study of Mitchell). However, when masker intensity is calculated as sensation level (SL) in each of these studies, it appears that for each pattern the sound intensity needed to mask tinnitus is lowest when masker frequency is in the frequency region where impairments of auditory function are present. Almost all participants in these studies report masking when presented with

sounds in this region (94% in the study of Mitchell, 1983).

The relation of masker frequency and intensity (SL) to hearing impairment implies that the frequency spectrum of tinnitus overlaps the frequency range where hearing loss is present. This is because it is in this frequency range that tinnitus sounds would be most confusable with the maskers. Evidence on this question is clouded to some degree by the fact that many studies measuring tinnitus frequencies have not measured the hearing threshold above 8 kHz. Another factor is that the frequency of tinnitus has often been measured by matching the tinnitus to pure tones that may not cover the bandwidth of the tinnitus. Fowler (1944) stated that even tinnitus that sounds like a pure tone is in fact always a narrow band of frequencies; Reed (1960) found that only ~1/4 of the participants in their studies were able to select a pure tone to match their sensation. Despite limitations such as these, Vernon and Meikle (2003) found that 75% of the participants in their studies reported tinnitus pitch matches above 3 kHz, which is the region where hearing impairments are most common. Noreña et al. (2002) measured tinnitus frequencies in participants with tonal tinnitus by presenting, one at a time, pure tones spanning the frequencies of the audiogram, including the region of hearing impairment up to 14 kHz. The participants in these studies were asked to state whether each pure tone corresponded to a component of their tinnitus, and if it did, to rate on a 10-point scale (10 = tinnitus) the extent to which the frequency was part of their tinnitus sensation. Results from four representative participants are reproduced in Fig. 1. In each of the 10 individuals tested (all reporting a tonal sound to their tinnitus), several frequencies were judged to resemble the tinnitus sensation, and these frequencies spanned the region of hearing impairment.

Psychoacoustic measurements presented by Noreña et al. suggest that even in tonal tinnitus it may be more appropriate to speak of the tinnitus “spectrum” than of the tinnitus “pitch.” The findings also imply a relation between the tinnitus spectrum, masking efficiency, and elevation of the hearing threshold. A relationship among these variables is expected if neural hypersynchrony in

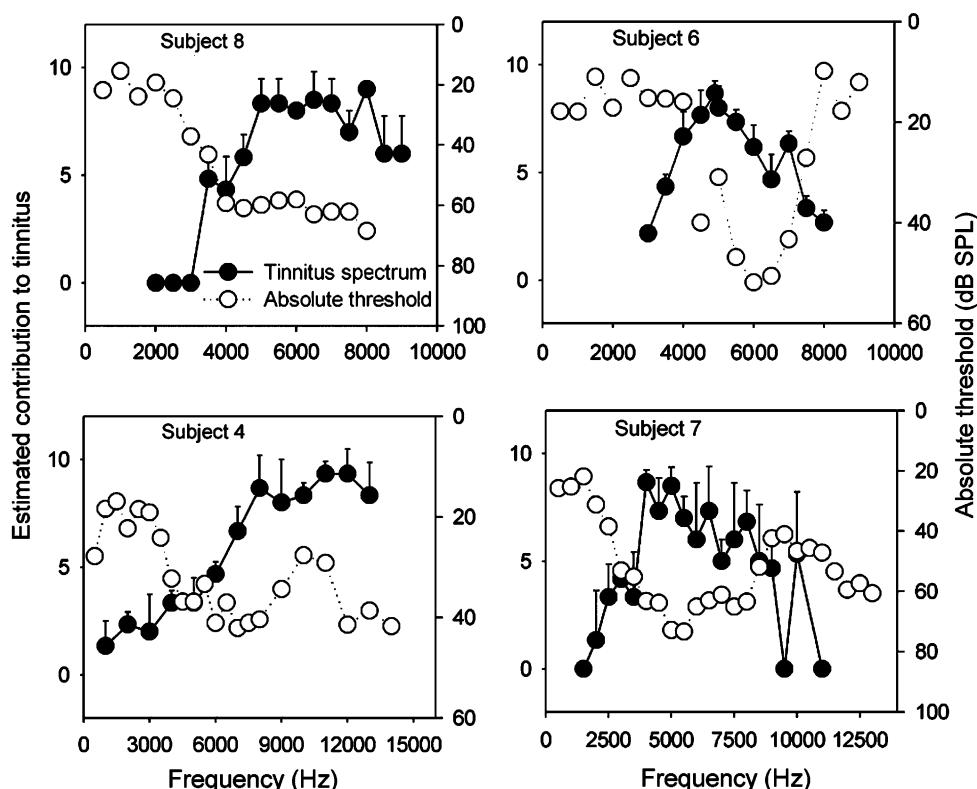


Fig. 1. Estimated tinnitus spectrum in relation to hearing loss in four individuals with tinnitus (adapted with permission from Noreña et al., 2002). The results are representative of 10 participants tested, all reporting tonal tinnitus. Etiology was auditory trauma (Participants 6 and 7), sudden hearing loss (Participant 4, tinnitus 1 year duration), or unknown (Participant 8, tinnitus 3 years duration). Hearing thresholds were measured in 500 Hz steps from 0.5 to 8 kHz (up to 14 kHz when hearing loss at 8 kHz did not exceed 70 dB HL) using a staircase method. After threshold determination, participants adjusted the intensity of tones within the studied frequency range (one randomly selected tone at a time) to match the loudness of their tinnitus. Participants then stated whether the frequency corresponded to one of the components of their tinnitus spectrum, and if it did, gave a rating on a 10-point scale (10 = tinnitus) of the extent to which the frequency was part of their tinnitus sensation. Tones were presented monaurally either to the tinnitus ear (Participants 4, 6, and 7, unilateral cases) or to the ear where tinnitus was most pronounced (Participant 8, bilateral case). In each of the 10 cases tested, the rated tinnitus spectrum spanned the region of hearing loss.

cortical regions affected by hearing impairment is the basis of tinnitus. Maskers are effective only when presented above individual sound thresholds (Vernon and Meikle, 2003). When a masker of sufficient intensity is presented in the region of hearing impairment, excitation is injected via thalamocortical pathways into the affected frequency region followed by comparatively stronger feedforward inhibition after one synaptic delay (Douglas and Martin, 1990; Cruikshank et al., 2007). Inhibition may serve to restrict synchronous activity induced by the masker to neurons that code for acoustic properties contained in the

sound, leading to its normal perception, which interferes with the perception of tinnitus. Concurrently, inhibition would be expected to disrupt the abnormal synchronous neural activity that is believed to underlie tinnitus, diminishing its perceptual salience (Eggermont and Roberts, 2004). By comparison, masking sounds presented at other frequencies (i.e., at frequencies outside of the cortical region affected by hearing loss) may leave the tinnitus relatively intact, because tinnitus is not generated in these frequency regions.

A challenge for this hypothesis is to explain properties of masking that do not appear to be

consistent with it. For example, it is well established that for many individuals with tinnitus, maskers outside the frequency region of hearing loss can suppress tinnitus if presented at high enough SLs (Feldman, 1971). How this may occur is not precisely known. However, neurons in the auditory cortex lose their frequency specificity at high sound intensities (Phillips et al., 1994), which suggests that input from normally silent diverging thalamocortical projections may convey inhibition to the affected frequency regions. Alternatively, masking may spread to higher frequencies at high stimulus intensities, based on basilar membrane mechanics. It has also been reported that masking is most efficient for sounds whose frequency is just below the dominant tinnitus frequency (Terry et al., 1983). Inhibition may be stronger at these frequencies where hearing may be relatively better preserved. Alternatively, given the challenge of tinnitus measurement, studies of the frequency specificity of masker efficiency may have some uncertainties.

Does RI reflect a temporary segregation of abnormal synchronous neural activity that persists beyond the duration of tinnitus masking? Clearly RI and tinnitus masking are related. Although estimates vary, the proportion of individuals with tinnitus who report some degree of RI is in excess of 75% (Vernon and Meikle, 2003; Roberts et al., 2006), which is in the same range as those reporting masking. RI requires the use of masking sounds that exceed the minimum masking level (MML; Terry et al., 1983); cases of RI without some degree of prior masking, while logically possible, have not been reported in the literature. RI depth and duration increase as masker intensity is raised to +20 dB MML (Terry et al., 1983; Tyler et al., 1984), revealing a dose–response relationship that is consistent with disruption of synchronous neural activity in auditory structures as its basis.

If segregation of synchronous activity in regions of hearing impairment is responsible for RI, functions relating the depth of RI to masker characteristics should asymptote in the region of hearing loss, as tinnitus spectra appear to do. Roberts et al. (2006, 2007) devised three computerized tools controlled by the participant to assess this prediction

for 59 individuals with bilateral tinnitus who had their hearing measured to 16 kHz. The first tool acquainted the participants with the computer interface and, by using participant-controlled sound clips, the concepts of loudness and pitch. The second tool assessed the properties of tinnitus. Participants classified their tinnitus as “tonal,” “ringing,” or “hissing” by selecting one of the three sounds with a center frequency (CF) of 5 kHz but differing in bandwidth (pure tone, or noise limited to $\pm 5\%$ or $\pm 15\%$ of CF, respectively). The spectrum of the tinnitus was then determined in frequency range from 0.5 to 12 kHz, using sounds with the bandwidth previously chosen by the participant to resemble their tinnitus. The third tool measured RI functions using 11 band-limited noise maskers ($\pm 15\%$ of CF, 30 s duration) with the same CFs used to measure the tinnitus spectra, as well as white noise. Masking level averaged +10 dB MML for CFs above 5 kHz; between-participant variation depended on the extent of hearing impairment and the capabilities of the sound delivery system. The results shown in Fig. 2A confirmed the expected relationships. Tinnitus spectra and RI functions increased commencing near the edge of normal hearing and spanned the region of hearing impairment, with some diminution at 12 kHz where masker intensity (SL) was attenuated owing to the depth of hearing loss. Band-limited maskers with CFs in the tinnitus region also induced significantly greater RI than did white noise. The dependence of RI on CF and hearing function is especially striking in cases of notched hearing impairment. One early such case assessed by the procedure of Roberts et al. is shown in Fig. 2B (Roberts and Platt, 1998 unpublished). This participant reported elimination of tinnitus for ~30 s for narrow band maskers with CFs near 5 kHz, which also corresponded the region of hearing impairment and the tinnitus sensation. Maskers with CFs outside the region of hearing impairment were not effective. Although participants of this kind are not common, they do exist (Bailey, 1979) and set the frequency dependence of RI and its relation to hearing impairment into sharp relief. Interestingly, Kitajima et al. (1987) reported that maskers with frequencies in the tinnitus spectrum notched out can produce

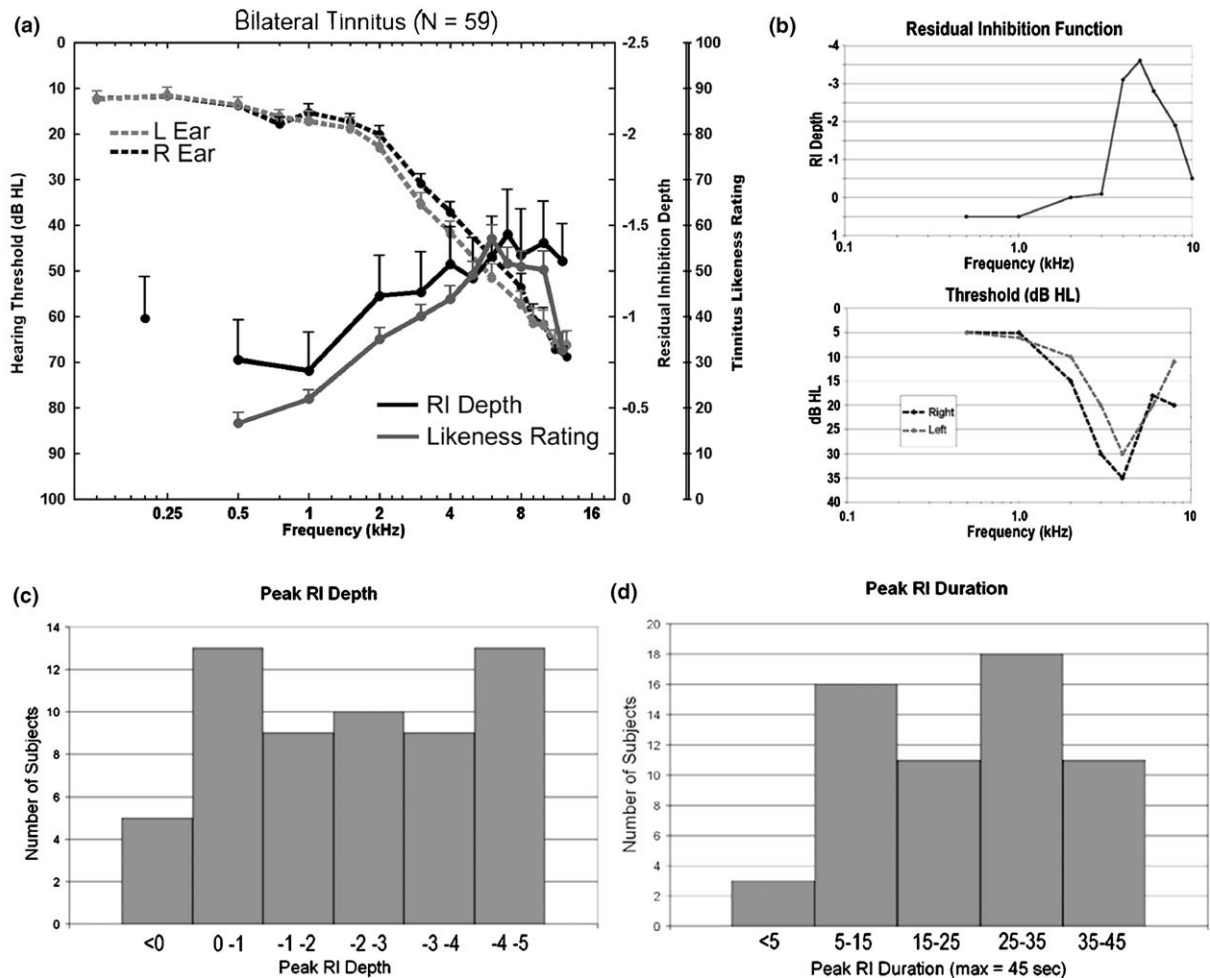


Fig. 2. Properties of residual inhibition. (a) Residual inhibition functions in relation to hearing loss and the tinnitus spectrum in bilateral tinnitus ($n = 59$ cases). RI induced by band-limited noise maskers ($\pm 15\%$ of CF) tracks the tinnitus spectrum and spans the region of hearing impairment. Each masking sound was presented for 30 s in a random order three times and followed by a rating of RI depth (-5 equals tinnitus elimination). RI depth induced by maskers with CFs above 4 kHz is greater than RI depth induced by white noise ($p < 0.028$, data point to the left). (Data from Roberts et al., 2006, 2007). (b) RI function (upper panel) in a participant with bilateral tinnitus and a well-defined notch at 4 kHz in the audiogram (lower panel). The tinnitus spectrum was described by narrow-band sounds with CFs centered at 4 kHz (data from Roberts and Platt, 1998, unpublished). (c) Frequency histogram of peak RI depth. Peak RI depth was determined as the deepest RI produced by the masking sounds used to measure the RI Function of Panel A (mean of three measurements). (d) Frequency histogram of peak RI duration (the longest duration RI at any masker, mean of three measurements). After each trial, RI testing resumed at 45 s (time-out limit) (data of C and D are from Roberts et al., 2007).

masking but induce less RI than their complements.

The RI functions shown in Figs. 2A, B are in qualitative agreement with the hypothesis that segregation of abnormal synchronous activity in a tinnitus network underlies RI. There is, however, considerable variability between participants in the

depth of RI and its duration, which, while it should not obscure significant main findings, needs to be understood. Some participants report near elimination of tinnitus for brief periods, and others only partial suppression. In the study of Roberts et al. (2007) 73% of participants reported some degree of RI, including 22% who described

elimination or near elimination of tinnitus following at least one of the maskers (see Fig. 2C). Peak durations however spanned a wide range, reaching the allowable limit of 45 s for at least one masker in 9 of 59 participants (15%, see Fig. 2D). While these results are in line with the literature, there are reports of RI lasting several minutes (Terry et al., 1983; Vernon and Meikle, 2003) or hours (Hazell and Wood, 1981). Some of this variability can likely be ascribed to the masking parameters loudness and spectral overlap described above, although functions relating RI depth to masker intensity appear to asymptote below +20 dB MML (Vernon, 1985; Roberts et al., 2007). Masker duration is also important. When maskers producing maximal RI at +10 dB MML were tested, Terry et al. (1983) found that RI duration increased linearly as a function of the logarithm of masker duration for durations between 10 s and 10 min. Thus very little RI was experienced for durations less than 10 s (cf. Tyler et al., 1984). Duration measured as full tinnitus recovery increased to ~100 s for maskers of 100 s duration, but to only 200 s for maskers ten times longer. On the other hand, ~43% of participants in the archive of Vernon and Meikle (2003) reported RI exceeding 2 min after 1 min of broadband noise (intensity unspecified). Four of 59 participants tested by Roberts et al. (2007) reported RI persisting 45 s (the maximum allowed before time-out) at all masker frequencies, suggesting that tinnitus was suppressed for the duration of RI testing (~1 h). Hazell and Wood (1981) reported that in a small percentage of their patients, 15 min of continuous masking gave RI lasting most of the day. To date, the factors that predict RI of long duration are not known. Standardization of methods would be helpful in charting tinnitus recovery functions more accurately and relating them to their determining conditions.

Although RI duration induced by current methods is typically brief, RI can be a source of relief for tinnitus sufferers who have experienced a sound that otherwise has known only a life of its own. Vernon and Meikle (2003) have described instances where patients broke into tears at their first experience of silent ears after years of unremitting noise. Hence there is much current interest

in optimizing RI for its possible clinical benefits. Following earlier studies by Feldman (1971), Terry et al. (1983) investigated whether refresher bursts of masking noise delivered during RI had a multiplicative effect on RI duration (they did not). Terry et al. (1983) also investigated in unilateral tinnitus cases whether maskers presented ipsilateral or contralateral to the tinnitus ear differed in their effectiveness. Only masking in the ipsilateral ear induced RI, implying convergence at some level in lemniscal projection pathways (75% of lemniscal fibers cross over above the level of the inferior colliculus). An alternative approach aims at engineering sounds that relate more closely to the participant's tinnitus. Commercial devices for tinnitus masking have begun to adopt this approach (<http://www.neuromonics.com>) although different methods of optimization are at present untested. Another approach explores how temporal and spectral variability may be exploited to enhance RI. In this respect it is noteworthy that tinnitus masking has been reported to be superior when noise stimuli are delivered independently to the two ears (dichotic stimulation) than when the same noise sound is presented to both ears (diotic stimulation; Johnson and Hughes, 1992). It is also important to assess whether continuous exposure to low intensity, high frequency background environmental sounds covering the region of hearing impairment can induce a lasting RI, particularly in new tinnitus cases. Noreña and Eggermont (2005, 2006) found that exposure to such sounds compared to low frequency sounds or to silence prevented hypersynchrony and cortical map reorganization that otherwise occurred in cats exposed to traumatic noise. This therapeutic effect appeared to be additional to changes in the auditory periphery, which partly restored normal hearing function (Noreña and Eggermont, 2005).

The duration of RI is of interest not only for clinical applications but also for understanding tinnitus. The perspective adopted for this chapter leads one to predict gradual recovery from tinnitus suppression, as synchronous networks resume their activity after masker offset. Recovery must reflect the time constants of neural processes that modulate the return of hypersynchrony (some candidates are discussed in the next section).

However, a practical limitation of RI for use in clinical applications relates to sound intensity level. For participants with deep hearing impairment, maskers presented at intensities needed to induce RI (+10 dB MML) may deliver sound pressures in excess of 100 dB to the ear. Continuous exposure to such sounds for extended lengths of time pose a risk of exacerbating peripheral hearing injury. Transcranial magnetic stimulation (TMS) may have an advantage in such cases, because its effects do not require the ear to reach the brain. TMS may induce some of its effects by mechanisms that are at work in RI. Because it can be directed to selected brain areas, TMS can also identify brain regions that form part of the tinnitus network.

Transcranial magnetic stimulation

TMS is a procedure through which a magnetic field is injected into the brain, inducing currents that cause cortical neurons within the field of rapidly changing magnetic flux to depolarize (see Chapters 34 and 35). Because this neural input occurs independently of synaptic events involved in ongoing network activity, it would be expected to disrupt the abnormal synchronous activity that is believed to underlie tinnitus, leading to its temporary suppression.

Both high frequency (10–20 Hz) and low frequency (1 Hz) magnetic stimulation delivered repetitively (rTMS) have been found to suppress tinnitus in a subset of cases, when applied to brain regions that are active in tinnitus. In a seminal study, [Plewnia et al. \(2003\)](#) applied trains of high-frequency rTMS (10 Hz, 3 s duration) to each of five cortical sites at 120% of motor threshold (MT, 100% equals the current intensity required to evoke finger movements). Eight of 14 (57%) tinnitus patients reported suppression of tinnitus ranging from partial to complete elimination for a period of time described as “transient” (one patient reported an increase in tinnitus). Tinnitus suppression was statistically enhanced when rTMS was delivered over left temporal and left temporal-parietal cortex compared to other regions. In a subsequent study ([Plewnia et al., 2007](#)), low

frequency rTMS (1 Hz) was navigated to a region of temporoparietal cortex that showed maximal activation determined by positron emission tomography (PET) imaging during prior lidocaine infusion for each participant, or to a control area in the lower occiput. Reduction of tinnitus was reported by six of eight participants, which lasted for 3–8 min and was larger than during sham stimulation. Tinnitus suppression was more robust for tinnitus cases of short duration (2–4 years) than for tinnitus of long standing (9–15 years), a relationship reported by [De Ridder et al. \(2005\)](#) as well (see Chapter 36).

Compared to RI that activates excitatory and inhibitory auditory pathways in a frequency selective fashion, the currents induced by rTMS in the targeted cortical structures are diffuse and non-specific. Nevertheless, similarities between RI and tinnitus suppression by rTMS suggest that disruption of abnormal synchronous neural activity may underlie suppression induced by both procedures. Suppression by rTMS persists for a variable range of durations, which is also true of RI. Suppression on the order of minutes found by [Plewnia et al. \(2007\)](#) do stand out compared to RI where reports of suppression lasting 15–45 s are more common. However, several investigators have reported RI lasting minutes and longer ([Hazell and Wood, 1981](#); [Terry et al., 1983](#); [Vernon and Meikle, 2003](#)). Like RI, tinnitus suppression by rTMS shows dose-dependent effects, increasing with the duration of stimulation ([Plewnia et al., 2007](#)) and with rTMS intensity ([De Ridder et al., 2004](#)). While direct comparisons between the results from RI and rTMS studies have not been published, rTMS studies concur that suppression of tinnitus by rTMS is consistently larger than suppression by sham stimulation alone ([Eichhammer et al., 2003](#); [Plewnia et al., 2003, 2007](#); [Kleinjung et al., 2005](#); [De Ridder et al., 2004, 2005](#)). Thus suppression by rTMS is more than simple RI induced by sounds that are generated by the device used to generate magnetic signals. Another feature common to both types of tinnitus suppression is that in both cases tinnitus does eventually return.

Whether RI maskers can achieve suppressive effects equal to rTMS cannot be determined on the basis of published findings, but can be questioned

given the strong intracortical currents injected by rTMS. These currents may induce plastic changes in synaptic efficacy (Cooke and Bliss, 2006) that have been demonstrated for motor responses when low frequency rTMS is paired with median nerve stimulation in humans (Huang et al., 2005). However, while sham stimulation does not yield as much tinnitus suppression as rTMS, the acoustic properties of sham stimuli including their intensity and spectra are not likely to resemble the tinnitus sensation which may be required for optimal RI. It is noteworthy that suppression of tinnitus by rTMS is greater for early cases of tinnitus than for long standing ones (De Ridder et al., 2005; Plewnia et al., 2007). To be effective, therapies based on rTMS (Eichhammer et al., 2003; De Ridder et al., 2004, 2005; Kleinjung et al., 2005) or RI (Watanabe et al., 1997) may have to intervene before functional plastic changes lead to structural ones (Pons et al., 1991; Muhlau et al., 2006).

Future questions

Our understanding of the mechanisms of tinnitus and its suppression would profit greatly from the development and standardization of tools for measuring the psychoacoustic properties of tinnitus including its loudness, spectrum, and suppression by maskers (RI) or rTMS. Fortunately, one can see a degree convergence in the procedures that are being developed for assessment of tinnitus spectra and RI functions by different laboratories (Noreña et al., 2002; Henry et al., 2006; Roberts et al., 2006; Ward et al., 2007). Future studies may provide what has been lacking, which is a systematic database against which to evaluate procedures for optimizing RI and contrasting it with rTMS and other methods of intervention using common measures.

Abbreviations

CF	center frequency
MML	minimum masking level
MT	motor threshold
PET	positron emission tomography
RI	residual inhibition

rTMS	repetitive transcranial magnetic stimulation
SL	sensation level
SPL	sound pressure level
TMS	transcranial magnetic stimulation

Acknowledgments

Supported by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the American Tinnitus Association. I thank Jos Eggermont and Aage Møller for their helpful comments regarding earlier versions of the manuscript.

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CHAPTER 48

Clinical trials for tinnitus: study populations, designs, measurement variables, and data analysis

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Abstract: We review a few issues related to clinical trials for treating patients with tinnitus, including the study population, design, choice of measurement variables, and some new approaches to data analysis. We emphasize the importance of being aware of different subgroups of tinnitus patients, and that patients who have had tinnitus for less than 6 months could be more amenable to treatment than patients who have had their tinnitus for a longer period. We distinguish the tinnitus itself, from the reactions to the tinnitus. When the treatment is intended to reduce the tinnitus, we recommend measuring the magnitude of the tinnitus. We provide arguments and data to support the use of the Tinnitus Handicap Questionnaire as a measure of the reaction to the tinnitus. We suggest that the current quality of life measures are not valid for measuring lifestyle effects of alleviating tinnitus. Because tinnitus likely has different subgroups, and because tinnitus affects people differently, we believe data analysis should emphasize individuals, not groups. A clinically meaningful effect should represent a valid and reliable statistical change for an individual.

Keywords: tinnitus; clinically significant; tinnitus handicap questionnaire; tinnitus severity; tinnitus measurement

Study population

Types of tinnitus

Tinnitus can be conductive or sensorineural, analogous to hearing loss (Tyler and Babin, 1993). Conductive (others prefer objective) tinnitus is transmitted to the cochlea by conduction in body tissue, and is typically of vascular or muscular cause whereas sensorineural (others prefer

subjective) tinnitus is not associated with a physical sound but caused by abnormal neural activity generated in the ear, the auditory nerve, or the central nervous system (see Chapter 1).

In the following sections we will focus on sensorineural tinnitus (although our comments can be applied to both forms). It is generally agreed that there are several kinds of sensorineural tinnitus but presently it is not clear how to distinguish between their different forms. Stouffer and Tyler (1990) estimated that approximately 1/3 of 528 tinnitus patients reported that their tinnitus was not present the entire day, and more than 20%

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reported it changed in pitch or loudness. Intermittent tinnitus can be even more annoying than continuous tinnitus if it is unpredictable. If tinnitus is intermittent or changing, it is necessary to quantify the magnitude of the tinnitus with multiple baseline measures and to consider the severity of tinnitus (before and after treatment) estimated over several days or weeks.

Exclusion criteria

Patients who cannot provide valid and reliable data should be excluded from studies. Obviously, it is important to ascertain as clearly as possible that any changes can be attributable to the treatment under study, and not due to some other variable. Therefore, patients undergoing other tinnitus treatments, such as counseling and sound therapies, medications, and dietary supplements should be excluded or required to stop treatment for a sufficient time. Similarly, patients facing other major health or lifestyle challenges, such as a major surgery, psychological counseling for depression, or divorce, should also be excluded.

Subgroups

Tinnitus is a symptom that may have many different causes and is likely coded in the nervous system by many different mechanisms. Therefore, any particular treatment may only be effective on a particular subgroup of individuals (Tyler, 1992).

Distinguishing between different subgroups of individuals with tinnitus is not self-evident, but likely include cause (e.g. noise, head injury, drug induced, aging), psychoacoustical behavior (e.g. post-masking categories or tonal masking patterns), and perceptions (tone-like vs. noise-like).

One subgroup might be patients who can modulate their tinnitus with muscular, proprioceptive, or perhaps visual stimulation (Cacace et al., 1999; Sanchez et al., 2002; Levine et al., 2003). We believe it is important to distinguish those modulations, which could be mediated by middle-ear muscle contraction (and therefore have their influence through the cochlea) from those maneuvers that are initiated by non-auditory neural

pathways at the cochlear nucleus and above (e.g. Møller et al., 1992; Kaltenbach et al., 2002; Shore, 2004).

Duration of tinnitus

There are two opposing matters in considering the duration of tinnitus as an inclusion criterion; (1) it is likely that the neural representation of tinnitus can more likely be altered if the treatment is applied as soon as possible after the neural code for the tinnitus is formed (see Chapter 2); and (2) there may be spontaneous recovery among some patients during the first few months. Additionally, even after the magnitude of the tinnitus becomes constant, the annoyance of the tinnitus can decrease over several months; an outcome sometimes termed “habituation”. The first consideration above suggests treating the patient as soon as possible. The second suggests excluding patients who have had tinnitus for less than about 1 year. We suggest treating the patient as soon as possible since it cannot be predicted which patients would experience spontaneous recovery, and by waiting an opportunity for successful treatment may be missed (see also Chapter 22). In a crossover design, and in a parallel group design, concerns about spontaneous recovery can be partially overcome by ensuring that the duration of tinnitus is matched across groups. We suspect that the number of patients with spontaneous recovery is small, and this consideration is offset by the potential to uncover a major effect of a treatment in patients with newly acquired tinnitus.

Crossover or parallel groups

When conducting tinnitus trials, crossover designs and parallel groups designs are often considered. In a crossover design, participants are recruited to receive multiple treatments. They will first receive one treatment where results are recorded. A wash-out period is then required to allow the first treatment to leave the subject’s system. After the washout, the subject receives the second treatment where results are recorded. The term ‘parallel groups’ represents two independent groups who

each receive separate treatments. There is no need for a washout period in this case.

A crossover design has many advantages over parallel groups. One of the biggest advantages is the ability to control for subject level variables. When a subject is able to serve at her or his own control, many extraneous variables that may have an impact on the group influence are accounted for, allowing the analysis to focus on the group effect. A crossover design also requires a smaller sample size for similar power. Only one group of participants needs to be recruited instead of two independent groups.

There are potential problems associated with a crossover design as well. First, the treatment might eliminate the tinnitus, so crossover is not possible. Second, the washout period might be unknown or very long. A very long washout period delays the study, and might increase dropouts or allow time-course natural changes to the tinnitus to arise.

It is important in parallel group designs to have an equal number of participants per group. This allows for one-to-one matching of the participants. Careful consideration is needed on the best approach to matching since it is not known how similar the matching must be and what are the important variables. Indeed, some important variables may not be known. For tinnitus, it is likely important to match on cause and duration of tinnitus, and possibly level of hearing loss. Of course, the degree of matching should be reported in publications.

Choice of measurement variables

A decision needs to be made whether the treatment is aimed at decreasing the tinnitus or the effects of the tinnitus. Figure 1 shows an adaptation of the model proposed by Dauman and Tyler (1992) to help conceptualize factors related to measuring and understanding tinnitus and its effects. The perception of the tinnitus (what it sounds like) leads to a reaction, but this reaction is influenced by an individual's psychology. Measures of the tinnitus itself are less influenced by these psychological factors.

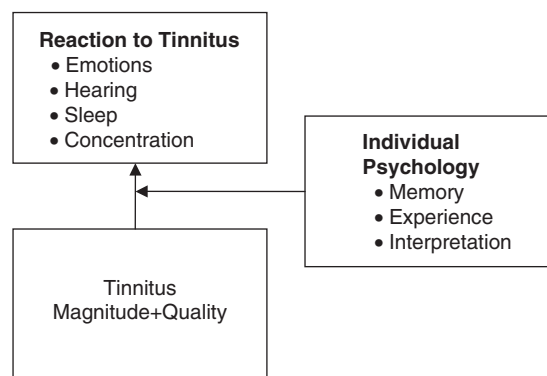


Fig. 1. Flowchart showing how the characteristics of tinnitus (its magnitude and quality) influence the reaction to the tinnitus, by are impacted by individual factors.

For an individual in a clinical trial, it should be expected that if the loudness of the tinnitus is decreased, it will be less annoying. Some have argued that the qualities (such as the loudness) of the tinnitus are unrelated to the annoyance. We believe this is not necessarily true. As Dauman and Tyler suggested, this relationship is influenced by the patient's psychology. Therefore, when examining the relationship across individuals the correlation is weak. But even then, patients who *report* that their tinnitus is louder tend to report their tinnitus as more annoying (see Fig. 2).

Any measurement must be valid (measure what it purports to measure), reliable, and sensitive (able to document changes). Objective measures, not requiring a judgment from the patient or experimenter, are not yet available for tinnitus. When objective measures are available, caution will be necessary as it is often difficult to interpret objective measures (their validity is unclear).

Primary measure

A single primary measurement is needed to determine if the treatment was effective, and if so, how effective. This should be decided before the clinical trial. Treatments are usually aimed at reducing the magnitude of the tinnitus (e.g. a drug treatment or electrical stimulation), or at reducing a patient's reaction to the tinnitus (e.g. a counseling

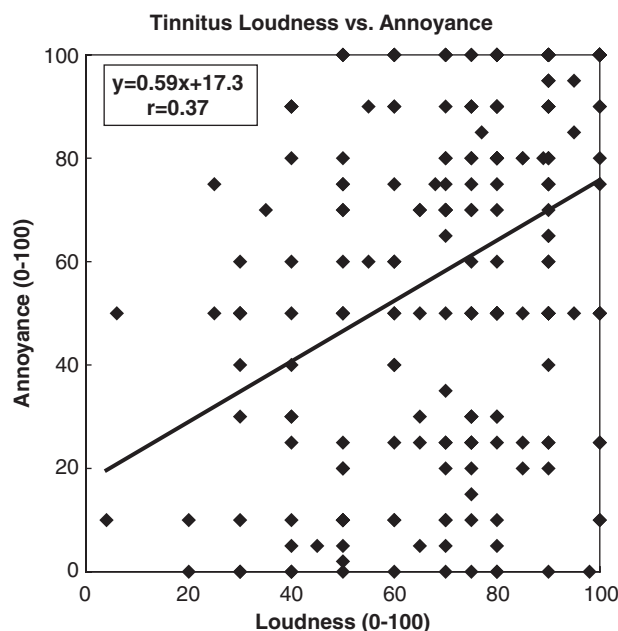


Fig. 2. The relationship between tinnitus loudness versus annoyance. Across different individuals, patients who rank their tinnitus as louder tend also to rank their tinnitus as more annoying. Individual difference in interpreting the scales, and individual psychological factors (see Fig. 1) influence this relationship when compared across individuals.

procedure). Measuring the reactions to the tinnitus are more likely to be influenced by non-treatment factors, and are less desirable when treatments are aimed at reducing the magnitude of the tinnitus.

Secondary measures

Secondary measures are not used to test the primary hypothesis. There might be a secondary hypothesis, for example that sleep problems are, or are not, affected by the treatment. Other common secondary measures might include depression, anxiety, or quality of life (see below). If the primary aim is to reduce the magnitude of the tinnitus, it would also be of interest to know if the reaction to the tinnitus is also reduced.

Predictor variables

In part because there are subgroups of tinnitus patients, it would be very useful to know which subgroups were most likely to benefit from

treatment. One approach is to select a large number of variables likely to separate tinnitus into groups, such as by etiology (e.g. noise, aging, head injury, drugs), biographical facts (e.g. age, gender), tinnitus history (e.g. ear, severity, duration), tinnitus quality (e.g. tonal, noise-like, rhythmic), and by the severity of depression and anxiety. [Stouffer and Tyler \(1990\)](#) provide such a questionnaire, as well as data from over 500 patients attending an otology/audiology clinic. Other variables might include the results of brain imaging and genetics.

Measures of the magnitude of the tinnitus

Options for measuring tinnitus magnitude include estimates of the minimum noise level required to mask the tinnitus or estimates of loudness. Masked thresholds, even for tinnitus, tend to have high test-retest reliability ([Small and Tyler, 1978](#)). This is a potential advantage over loudness measurements. However, the tinnitus of some patients

Table 1. Suggested single questions to evaluate loudness, annoyance, and the percentage of time tinnitus is present

1. Loudness

I want you to rate the loudness of your tinnitus during the last 2 weeks on a scale from 0 to 100; 0 representing the softest tinnitus you can imagine and 100 representing the loudest tinnitus you can imagine. Intermediate numbers represent intermediate loudness ratings.

2. Annoyance

I want you to rate the annoyance of your tinnitus during the last 2 weeks on a scale from 0 to 100; 0 representing the least annoying tinnitus you can imagine and 100 representing the most annoying tinnitus you can imagine. Intermediate numbers represent intermediate annoyance ratings.

3. Percentage of time present

During the time you are awake, what percentage of time is your tinnitus present?

Assign a value from 0 to 100%.

Source: Adapted from Stouffer and Tyler (1990).

cannot be masked at all (e.g. Tyler et al., 1984) and this would result in missing data. Two options for quantifying the loudness of tinnitus include using responses to questions (e.g. ratings from 0 to 100 of loudness or an equivalent visual analog scale) (see Table 1), or results of loudness balancing between the tinnitus and a matching signal (perhaps converting to sones) (e.g. Tyler and Conrad-Armes, 1983; Henry et al., 1999). Changes in hearing threshold might influence the interpretation of these test results, and it is therefore necessary to measure the thresholds to the test stimuli.

Measures of the reaction to tinnitus

Assessing patients' reactions to their tinnitus could be approached by either single questions or questionnaires.

For single questions, we suggest a focus on *loudness* and *annoyance* (consistent with Fig. 1) (Table 1). The term severity could be applied to either loudness or annoyance, but would be difficult to interpret. Stouffer and Tyler (1990) also suggested two other measures; the percentage of time tinnitus was present during the time awake, and the days per month that tinnitus is bothersome.

Using a scale from 0 to 100 is similar to using a visual analog scale, but has the practical advantage that it is not necessary to measure the distance

along a line. Patients are also familiar with the decimal system and this is an advantage over some questionnaires, where patients may have difficulty interpreting labeled scoring options. Handscomb (2006) reported that more than 1/3 of patients either filled in the Tinnitus Handicap Inventory (Newman et al., 1996) questionnaire incorrectly or not at all!

Another useful approach is to use individual questions from established questionnaires. This approach is illustrated in Fig. 3, which also compares the advantages in sensitivity of a 0–100 interval scale compared to a 3-point ordinal scale. We have selected individual patient data, combined from several studies in progress, showing pre-treatment and 6-month post-treatment scores on some individual questions of the Tinnitus Handicap Questionnaire (Kuk et al., 1990) and Tinnitus Handicap Inventory (Newman et al., 1998). We have selected single questions on concentration (Figs. 3a, b), hearing (Figs. 3c, d), and sleep (Figs. 3e, f). To the right of each panel, individual results are shown for patients who have multiple measures over time. In each pair of panels, the larger scale and better sensitivity of the Tinnitus Handicap Questionnaire allows the observation of smaller changes. Whenever an individual question is used, it is necessary to establish test–retest reliability.

Several questionnaires have been developed for tinnitus (see reviews by Tyler, 1993 and Noble, 1998). We believe the Tinnitus Handicap Questionnaire (Kuk et al., 1990) is perhaps the most widely used (e.g. Dobie et al., 1992; Dauman et al., 1993; Newman et al., 1994, 1995; Meric et al., 1997, 1998; Henry and Wilson, 1998; Higgins et al., 2002; Mrena et al., 2002; Bouscau-Faure et al., 2003; Henry et al., 2003, 2006; Robinson et al., 2003, 2005; Londero et al., 2006) and has been translated into other languages (e.g. Meric et al., 1997; Bouscau-Faure et al., 2003). This questionnaire was developed in two stages. First 87 questions were administered to 100 patients. Second, based on sensitivity and independence, a subset of questions was then tested on 319 patients. Also unlike other questionnaires, the test–retest reliability was evaluated by independent studies (e.g. Newman et al., 1995).

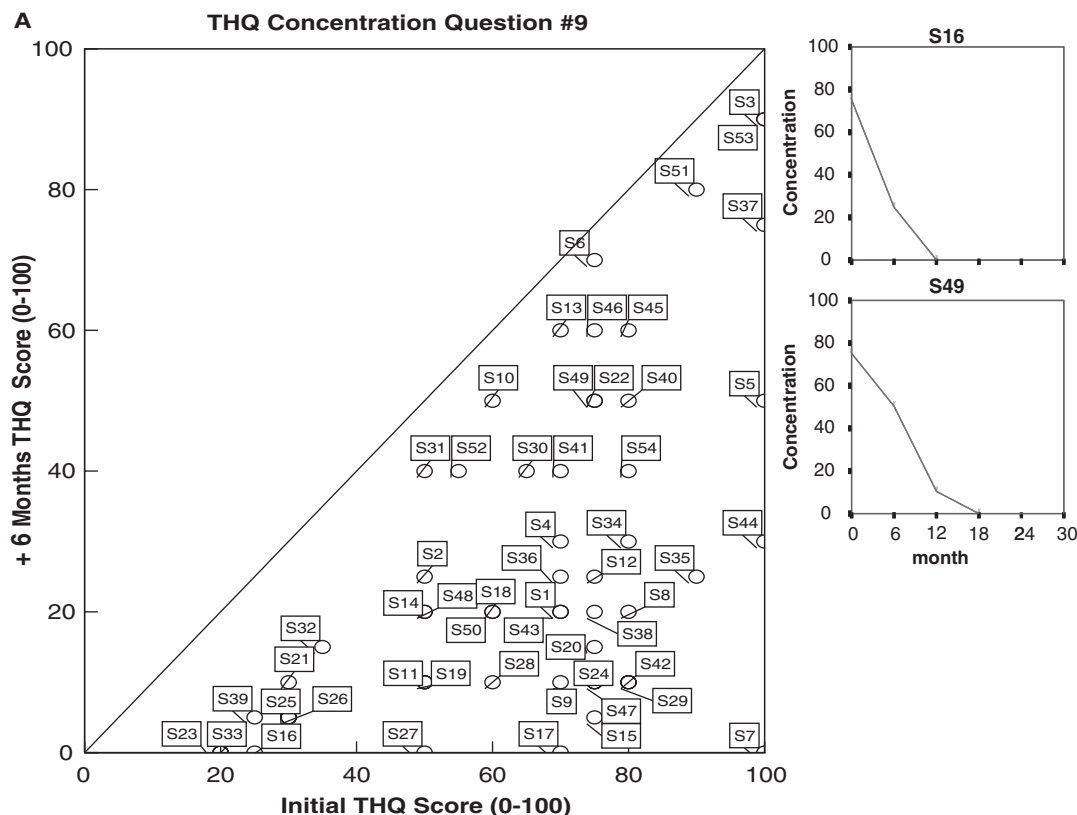


Fig. 3. Responses to individual questions on the THQ and THI before and after counseling and sound therapy. In each panel, the left scattergram shows scores pre and post 6-months treatment. The right figures show performance over time for two individuals. (A) THQ concentration question no. 9. (B) THI concentration question no. 1. (Yes to Yes: S3 S4 S6 S13 S37 S40 S51; Sometimes to Sometimes: S2 S8 S9 S10 S14 S27 S29 S32 S39 S41 S42 S43 S48 S50 S52; No to No: S11 S26; Yes to No: S7 S17; Yes to Sometimes: S1 S5 S19 S20 S22 S28 S30 S31 S34 S35 S36 S38 S44 S46 S47 S49 S53 S54; Sometimes to No: S12 S15 S16 S18 S21 S23 S24 S25 S33 S45). (C) THQ hearing question no. 4. (D) THI hearing question no. 2. (Yes to Yes: S1 S3 S9 S12 S14 S27 S36; Sometimes to Sometimes: S2 S7 S13 S17 S19 S24 S31 S34. No to No: S25; Yes to No: S15 S16 S22 S30 S40; Yes to Sometimes: S4 S5 S6 S11 S18 S20 S23 S33 S35 S37 S39 S41. No to Sometimes: S21; Sometimes to No: S8 S10 S26 S28 S29 S32 S38). (E) THQ sleep question no. 16. (F) THI sleep question no. 7.

Quality of life questionnaires

An effective treatment should ultimately impact on the patients' quality of life. However, we believe that the primary measure should be the tinnitus or its effects because there are other variables affecting the patients' emotions and social life (true for all of us). For example, the tinnitus magnitude and annoyance might have decreased, but because the person was involved in a car accident or got in a fight with friends that week, the impact of the effectiveness of the treatment was not observed. The influence of other confounding variables is

greatest the furthest away one moves from the tinnitus magnitude.

A second concern about these quality of life measures is their validity. How does one know which questions are relevant to the quality of life? In our opinion, several of the questions in many of these scales focus on mobility and self care. How might their validity be understood in the context of tinnitus? These are difficult questions. If we use quality of life measures that do not have appropriate validity, we could make serious mistakes in the interpretation of the results of tests using such questionnaires. We suggest not using quality of life

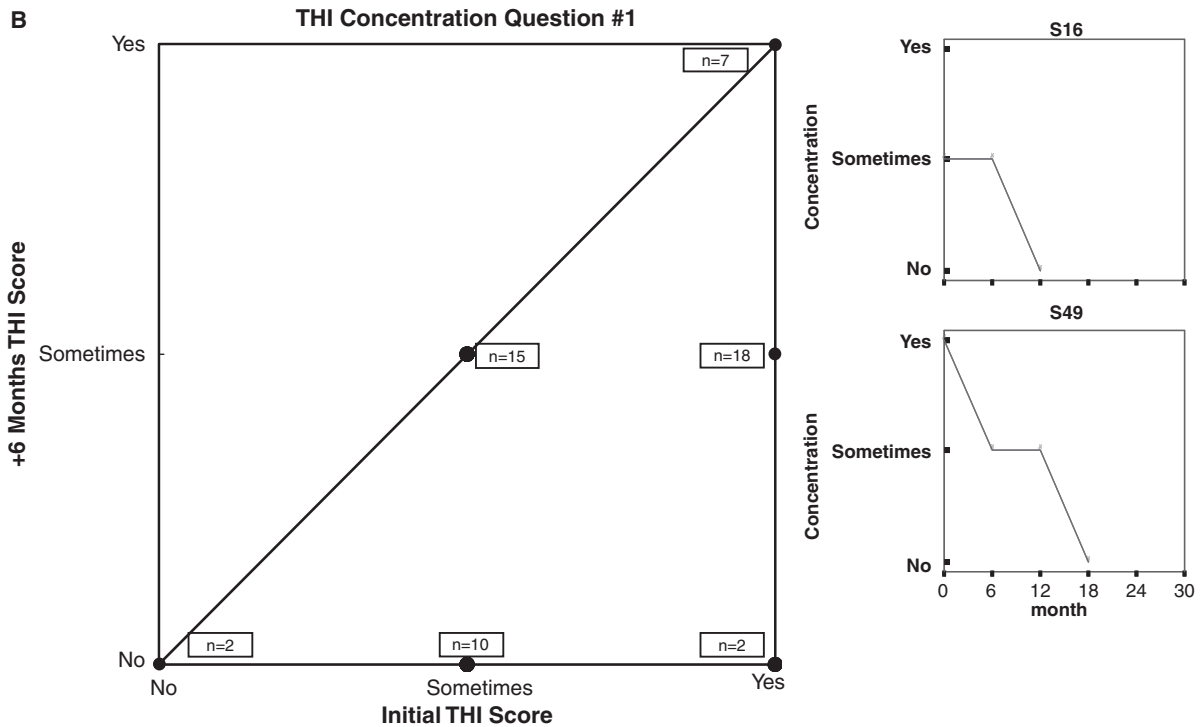


Fig. 3 (Continued)

measures until convincing data can be presented regarding validity.

Data analysis

Group versus individual data

There is a long-standard accepted approach to hypothesis testing that compares averages of groups. The assumption is that differences across participants are due to individual variation and measurement error. In an ideal world everyone would react the same way to the given treatment. We know in practice with tinnitus patients that individuals do not react the same as their prior data tells us they should. With the large degree of individual variation, group level statistical significance is difficult to attain unless there are large data sets. The standard hypothesis testing based on groups provides guidance regarding the power, effect size to be expected, and number of participants needed within a group to determine differences between

groups. There are instances, however, when individual data is much more informative.

It might be considered blasphemy to suggest that data analysis based on group statistics might not always be appropriate. The tinnitus of different patients may very well be different. The causes and mechanisms of the tinnitus differ and patients' reactions are different. We believe that it is more appropriate to examine individual results than group results. As an alternative, one could focus on the number of patients who benefited from a procedure. If important, one could specify the number of patients who were helped by a certain amount. In this context it is important to ascertain what constitutes a significant improvement for an individual.

Clinically relevant effect

People often attempt to distinguish a clinically relevant effect from a statistically significant one.

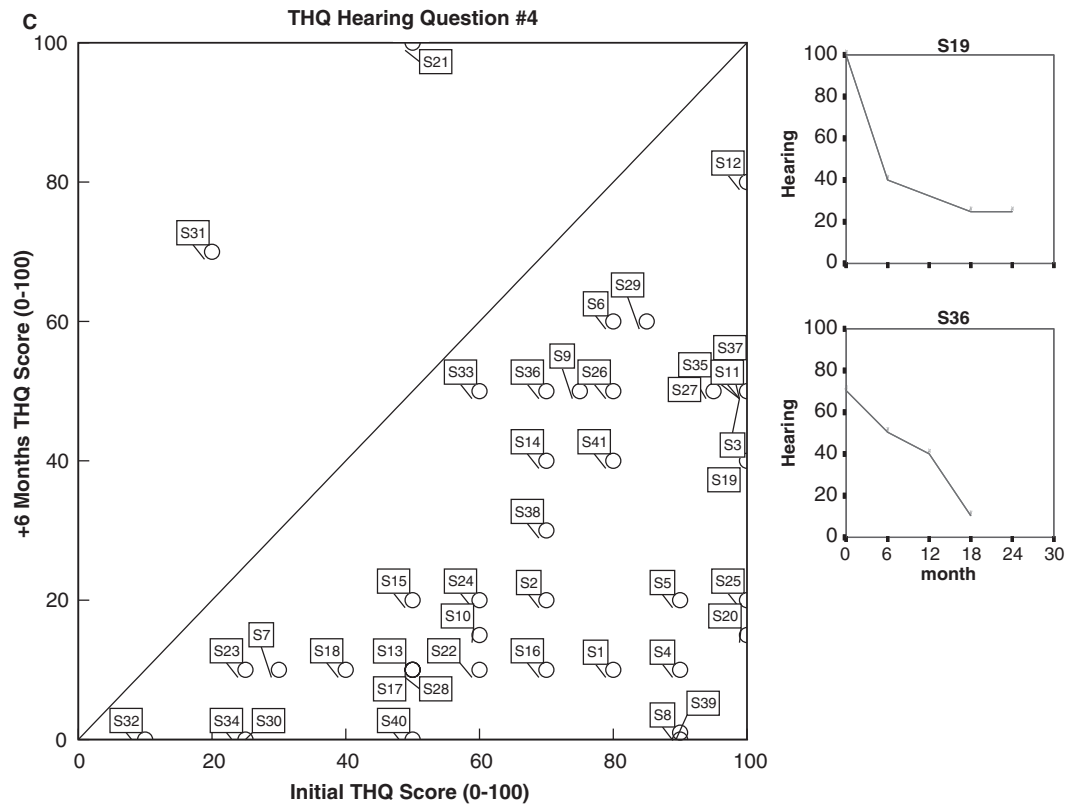


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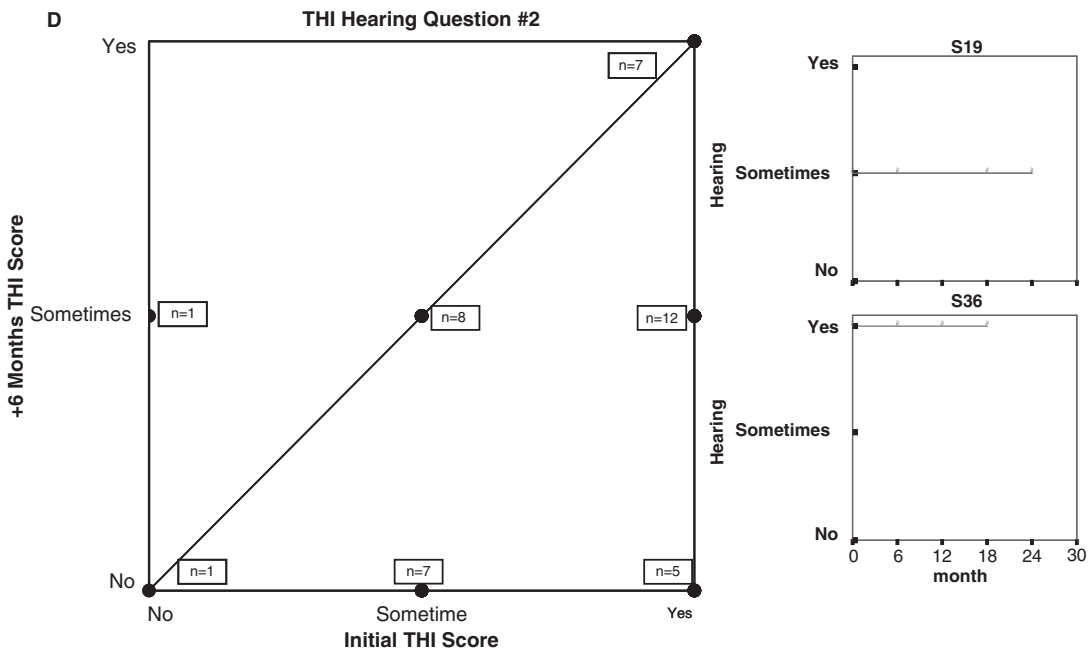


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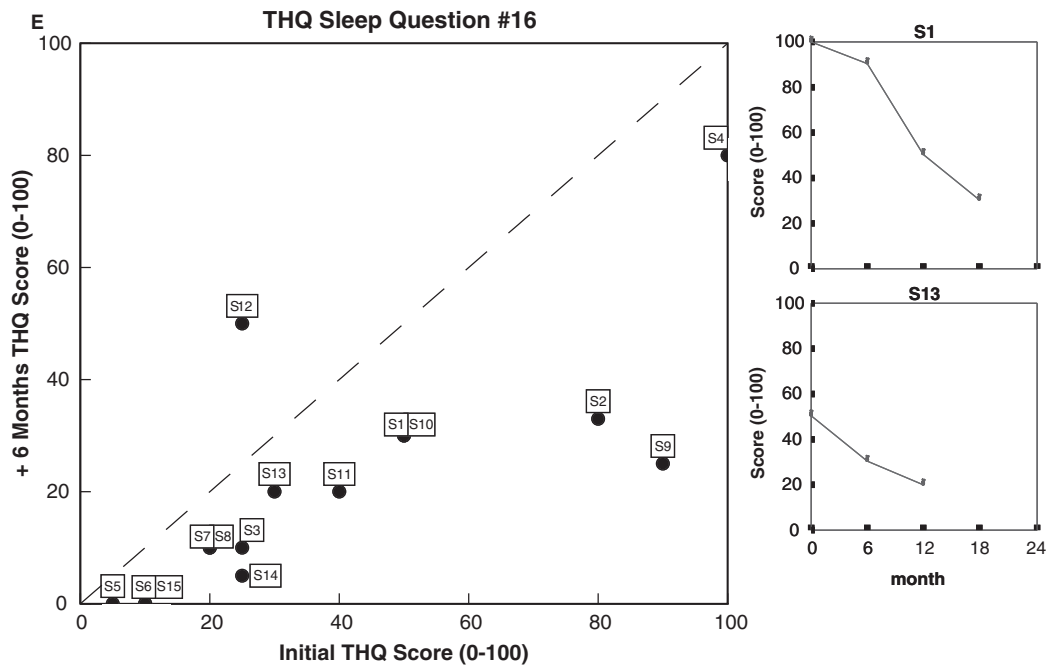


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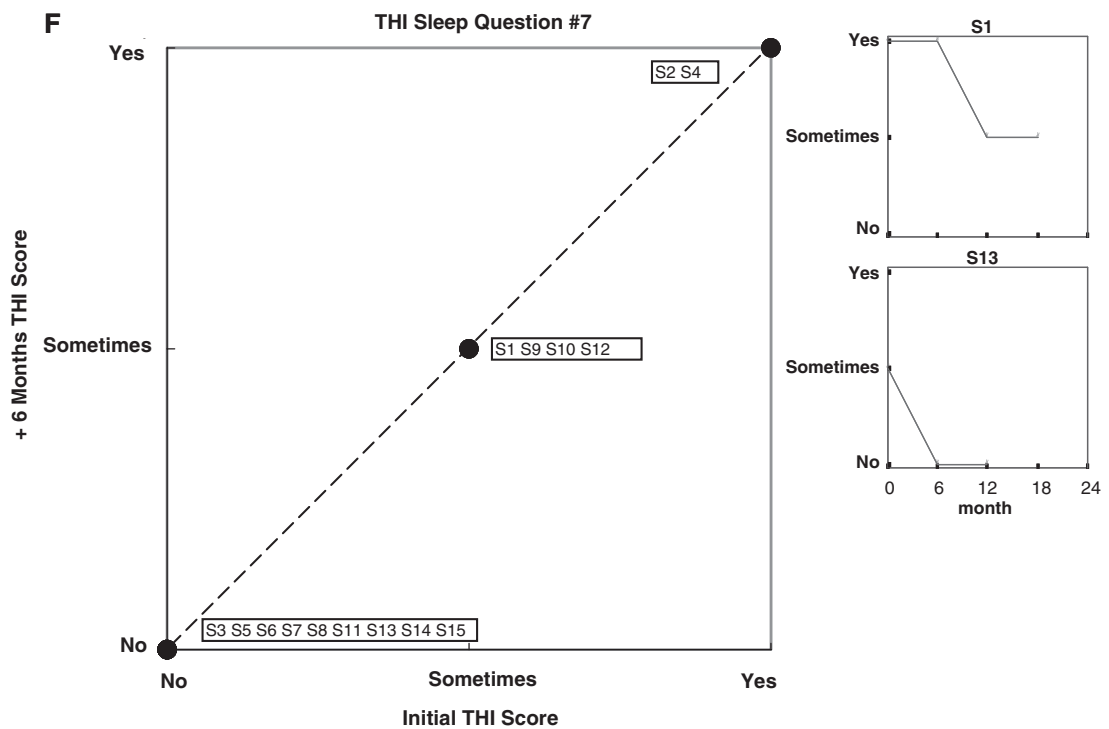


Fig. 3 (Continued)

This issue seems to arise in part from the analysis of group data. As the number of participants increases, the standard error decreases, and the test score required to reach statistical significance becomes smaller. People ask whether these small significant differences are really clinically relevant.

We believe this is the wrong question, and arises from confusion about individual versus group effects. In the example above, the statistical test is evaluating the likelihood that the scores arose from two different groups. A statistically significant difference between groups suggests that the groups are different. Of course, what is considered "significant" often depends on which statistical methods are used.

A different approach to this issue is to consider the validity of the questionnaire. If the questionnaire is designed to measure clinically real issues and it is valid, then we believe that a statistically significant difference for an individual is (by definition) clinically meaningful.

Acknowledgments

We wish to acknowledge grant support provided by the American Tinnitus Association and the National Institutes of Health (NIH Grant 5R01DC005972-02).

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CHAPTER 49

Assessment of tinnitus: measurement of treatment outcomes

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Abstract: There is a wide range of assessment techniques for tinnitus, but no consensus has developed concerning how best to measure either the presenting features of tinnitus or the effects of tinnitus treatments. Standardization of reliable and valid tinnitus measures would provide many advantages including improving the uniformity of diagnostic and screening criteria between clinics and facilitating comparison of treatment outcomes obtained at different sites. This chapter attempts to clarify issues involved in developing self-report questionnaires for the assessment of tinnitus. While the tinnitus questionnaires that are currently available provide valuable information on which to base diagnostic and screening decisions, they were not originally developed in such a way as to maximize their sensitivity to treatment-related changes in tinnitus. As a result, their construct validity for measuring treatment benefit has not received appropriate attention. In this paper, special emphasis is devoted to the use of effect sizes as an estimate of the ability of questionnaires (and their individual items) to measure changes associated with treatment. We discuss the criteria relevant to evaluating the effectiveness of a questionnaire for diagnostic purposes vs. for treatment-evaluation purposes, and we present a detailed illustration of how the various criteria have been applied in a recent questionnaire development effort.

Keywords: tinnitus severity; tinnitus questionnaires; self-assessment measures; tinnitus outcome measures; standardized tinnitus measures; tinnitus functional effects

The need for standardized tinnitus measures

Assessment of tinnitus for clinical or research purposes is a challenging task because of the subjective nature of tinnitus. Tinnitus researchers and clinicians have risen to that challenge over the past 20 years by developing a wide range of assessment

techniques. However, no consensus has developed concerning how best to measure either the presenting features of tinnitus or the effects of treatment. The variety of different measures has made it difficult to compare results obtained at different clinics. For that reason, a recent suggestion was to develop “a widely-accepted ‘core set’ of variables that can be used as a standardized evaluation protocol in clinical tinnitus research” (Meikle and Griest, 2002).

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Tinnitus research and clinical management would benefit greatly from standardization of measures used to characterize the severity and negative impact of tinnitus (Dobie, 2002; Turk, 2002). Similar issues apply in the management of another subjective condition, pain, which is well known to cause much distress and disability: A recent report describes efforts to develop a core set of information for use in measuring the clinical impact of pain on affected individuals (Turk et al., 2003). As stated in that report,

Development of a core set of outcome domains would facilitate comparison and pooling of data, encourage more complete reporting of outcomes, simplify the preparation and review of research proposals and manuscripts, and allow clinicians to make informed decisions regarding the risks and benefits of treatment.

Those statements are equally applicable to clinical measures of tinnitus. In addition, standardization of valid and reliable tinnitus measures would (1) provide more uniform diagnostic and screening criteria between clinics and even between different health providers in the same clinic; (2) provide a more systematic basis for defining selection criteria and then recruiting subjects into different treatment groups; and (3) facilitate comparison of treatment outcomes between different treatment modalities and between different treatment centers.

In this paper we will attempt to clarify some of the issues involved in designing the content and structure of self-report questionnaires for tinnitus that might satisfy the various clinical and research needs — that is, in addition to having high reliability and ease of use, they should (1) have high validity for measuring the severity and negative impact of tinnitus; and (2) at the same time should achieve high validity for measuring treatment-related changes in tinnitus.

Evidence-based management of tinnitus: what has been achieved so far

Recently there has been increasing awareness of the need for evidence-based selection of treatment methods in all areas of medical practice (Piccirillo, 1994;

Feussner, 1998). Similar concerns have been recognized in an audiological context (Cox et al., 2000; Gatehouse, 2000), and have also received attention by researchers and clinicians working with tinnitus (Erlandsson, 1992; Axelsson et al, 1993; Dobie, 2002; Turk, 2002). As mentioned above, a substantial literature has accumulated concerning self-assessment measures designed to scale the severity and negative impact of tinnitus (e.g., Newman and Jacobson, 1993; Newman et al., 1998). Among the major contributions to that literature are the nine questionnaires listed in Table 1, which were discussed in detail in several recent surveys (Meikle and Griest, 2002; Newman and Sandridge, 2004).

Taken as a group, these nine questionnaires identify a number of important dimensions that characterize the complex construct “tinnitus severity” in terms of its subjective, sensory aspects, as well as patients’ behavioral and emotional reactions to tinnitus (Table 2). As Table 2 shows, there is considerable overlap between the questionnaires in regard to the topics covered. It should also be noted that no single questionnaire covers all of the relevant tinnitus dimensions shown in Table 2.

Because these nine questionnaires reflect the combined experience and well-developed clinical judgments of tinnitus experts located in the United States, the United Kingdom, and Australia, they represent a valuable store of information about clinically significant tinnitus. They can thus provide important guidance in framing a new, more comprehensive tinnitus questionnaire that would have even higher construct validity for measuring the severity and negative impact(s) of tinnitus.

Turning to the need for measuring treatment effects, it is important to note that these existing tinnitus questionnaires were developed primarily with regard to their effectiveness for use as diagnostic and screening tools — primarily to assess the need for treatment and to guide clinical decisions regarding specific treatment modalities to be attempted in any given case. There has been a tacit assumption that such questionnaires can function well as outcome measures (i.e., to measure treatment-related changes). However, that assumption is questionable because none of the questionnaires were developed with explicit attention to maximizing their responsiveness to treatment effects.

Table 1. Nine widely used tinnitus questionnaires^a

Questionnaire name	Authors and year	Number of items	Response options for each item
Tinnitus Questionnaire	Hallam et al. (1988)	34	3 levels: true, partly true, not true
Tinnitus Handicap Questionnaire	Kuk et al. (1990)	27	100 levels: 100 = strongly agree, 0 = strongly disagree
Tinnitus Severity Scale	Sweetow and Levy (1990)	15	4 levels: wording of response options varies between items
Subjective Tinnitus Severity Scale	Halford and Anderson (1991)	16	2 levels: yes/no
Tinnitus Reaction Questionnaire	Wilson et al. (1991)	26	5 levels: not at all, a little of the time, some of the time, a good deal of the time, almost all the time
Tinnitus Severity Grading	Coles et al. (1992)	9	5 levels: wording of response options varies between items
Tinnitus Severity Index	Meikle (1992) and Meikle et al. (1995)	12	5 levels ^b : never, rarely, sometimes, usually, always
Tinnitus Handicap Inventory	Newman et al. (1996)	25	3 levels: yes, sometimes, no
Intake Interview for Tinnitus Retraining Therapy	Jastreboff and Jastreboff (1999)	12	7 items: 3 levels (always, sometimes, never); 2 items: 100 levels: 0–100% of time; 3 items: 0–10 numeric scale

^aEach of the nine questionnaires is cited in a separate bibliographic entry (see References).

^bOriginal version of Tinnitus Severity Index used more complex response options: six items had three levels, six items had four levels with wording of response options varying between items.

Table 2. Topics covered by the nine questionnaires in Table 1^a

Tinnitus topics or “dimensions”	Number of questionnaires that addressed the topic
Sleep disturbance	9
Intrusive, aversive nature of tinnitus	8
Irritability, nervousness, stress, tension	8
Reduced quality of life	8
Cognitive difficulty: problems concentrating, difficulty focusing attention, mental confusion	8
Difficulty relaxing: difficulty doing quiet leisure pursuits	7
Interference with social interactions and activities	6
Depression, feeling low, suicidal thoughts	6
Anxiety, worry, panic	6
Work interference	4
Hearing difficulties attributed to tinnitus	4
Anger, annoyance, frustration	4
Feeling uncomfortable in quiet	4
Reduced sense of control (feel insecure, helpless, desperate, unable to cope)	4
Feeling tired: ill, fatigued	3
Uncomfortable in noise, avoiding noise	3
Distress, general unhappiness	2
Ease of masking tinnitus by external sounds	2
Frequency of complaining about tinnitus	2

^aOmitted from list are topics mentioned in only one questionnaire: intermittency of tinnitus; worry that tinnitus may damage health; need for or use of medications for tinnitus; attitudes of others about tinnitus; tinnitus that is worse under stress; tinnitus has grown worse over years.

Evidence-based treatment or management of severe tinnitus is an increasingly important goal, and the existing store of tinnitus questionnaires provides a wealth of material on which to base a new generation of assessment instruments that will address the emerging needs of clinicians and researchers. It is therefore important to consider how our existing measurement tools might be reshaped to provide increases in comprehensiveness, precision, and sensitivity to treatment effects. For these reasons, it is now appropriate to consider how to design tinnitus measures that are optimized not only for screening and diagnosis, but also for evaluating treatment outcomes.

What measurement science can teach us: discriminative vs. evaluative measures

There is now considerable work concerning measurement techniques for evaluating treatment effects in a variety of healthcare situations (e.g., Kirshner and Guyatt, 1985; Lipsey, 1990; Farrar, 2000). In the body of research published by Guyatt and his colleagues, an important conclusion concerns content validity and how that relates to a questionnaire's intended use: Measures that perform well for diagnostic purposes may need to address a different range of topics (a different domain of information) than that appropriate for measures designed to evaluate treatment outcomes. The primary function of diagnostic or "intake" questionnaires is to characterize individual differences between patients in order to establish the clinical status and therapeutic needs in any given case. Such efforts have been designated as *discriminative* (Kirshner and Guyatt, 1985). Examples might include discriminating between individuals with severe vs. mild tinnitus, or identifying those individuals whose tinnitus triggers significant depression or who suffer from sleep interference due to tinnitus (Henry et al., 2002a).

An entirely different function is required for questionnaires used as treatment outcome measures. Outcome measures must be able to register change — in particular, treatment-related change — an aspect of measurement instruments that has been characterized as *evaluative* (Kirshner and Guyatt,

1985). Table 3 summarizes some of the main differences between questionnaires designed for discriminative purposes vs. those designed for evaluating treatment outcomes. The differences highlighted in Table 3 are important because they have a direct bearing on the ability of the questionnaire to measure successful outcomes in clinical trials.

For evaluating treatment outcomes, the domain of information that is sampled (the questionnaire content) should be limited to items that are responsive, that is, likely to change with treatment. Inclusion of non-responsive questions can reduce the ability of the questionnaire to detect real treatment effects. Clearly, that possibility should be avoided — inclusion of questionnaire items that are insensitive to change causes real treatment effects to be obscured or "diluted" by the presence of insensitive items. The net effect will be to require a larger sample of subjects in order to detect any statistically significant treatment effects (Lipsey, 1990; Schunemann et al., 2003). The bottom line is that less-responsive outcomes measures will increase the costs and lessen the efficiency of clinical trials.

For the nine English-language tinnitus questionnaires referred to above, the reported methods for the development of these questionnaires employed techniques that involved time-honored and well-established methods for developing diagnostic instruments: high test-retest reliability, high internal consistency reliability, and high content and construct validity for capturing between-subject differences. Desirable as such methods are for discriminative purposes, they are not adequate for ensuring measures that will be responsive to treatment-related changes in tinnitus. For outcomes measures, the primary concern must be to measure those aspects of the condition that are likely to change as a result of the treatment (Stewart and Archbold, 1992, 1993).

Effect size: an important parameter for outcome measures

A commonly used measure for quantifying treatment effects is the *effect size*, a measure that expresses the observed treatment effect in terms of standard deviation units of the item or scale in

Table 3. Important aspects of questionnaire construction^a

Key aspects of constructing health-related questionnaire	Discriminative (diagnostic) questionnaires	Evaluative (outcomes) questionnaires
1. Item selection	Responses of different patients or subjects should be heterogeneous (spread widely across the response continuum).	Lack of response heterogeneity is not a problem, may even improve an item's ability to show clear changes resulting from treatment.
2. Item reduction	Items that most subjects answer the same are unable to reveal diagnostic differences and should be deleted.	Delete any items that testing reveals are insensitive to change (regardless of whether they are sensitive to diagnostic differences).
3. Item response scaling	The chosen scaling should facilitate uniform interpretation by subjects (wording should not be ambiguous or confusing). Too much resolution may decrease subjects' response reliability.	An item's sensitivity to change is generally proportional to the number of response options it provides. Response scales should have high resolution (sufficient gradations) to register changes even if small.
4. Test-retest reliability	Within-subject variance should be small, between-subject variance should be large and stable (reliably indicating stable individual differences).	Within-subject variance should be small when functional status remains constant, but show large changes in scores when functional status improves.
5. Content validity	All or most of the important dimensions of the health problem should be addressed.	Address only those dimensions capable of showing treatment-related change.
6. Construct validity	Questionnaire scores should be highly correlated with well-established, comparable measures administered at that same time.	Questionnaire scores after treatment should bear the predicted relationship to the same measures administered before treatment.

^aContent of Table 3 is based in large part on information contained in: Kirshner and Guyatt (1985) and Stewart and Archbold (1992, 1993).

question (Lipsey, 1990; Stewart and Archbold, 1992). Effect sizes for treatment trials involving pre-treatment vs. post-treatment scores are calculated as follows:

$$\text{Effect size} = \frac{\text{Mean difference score for group}}{\text{Standard deviation of difference scores}}$$

For treatment trials in which an intervention group is compared with a control group, effect sizes are computed as follows:

$$\text{Effect size} = \frac{\text{Intervention group mean} - \text{Control group mean}}{\text{Average standard deviation}}$$

Effect sizes can be computed for each of the individual items in a given questionnaire, or for the overall scores obtained using that same questionnaire. The use of effect sizes provides an unbiased comparison by standardizing the mean score for a group in terms of that group's standard deviation. It is clear that effect sizes will be larger when there are large treatment effects (large

numerator), and will be smaller when there is much variability in the measured scores (large standard deviations, leading to a large denominator). A number of factors can influence effect sizes, including the measurement resolution (number of response options available for any given question), the specific nature of the treatment, and the extent to which subjects comply with that treatment (Lipsey, 1990). In general, effect sizes of about 0.20 are considered small; those around 0.50 are considered moderate; and effect sizes at or above 0.80 are considered large (Cohen, 1988).

Lipsey (1990) has emphasized the importance of maximizing effect sizes in order to increase the statistical power of studies such as clinical trials. Measures with inadequate effect size not only increase research costs by requiring larger sample sizes in order to detect a significant treatment effect, they also can result in failure to detect a real treatment effect when one has occurred. Although there is little evidence that previous efforts to develop tinnitus questionnaires involved consideration of effect sizes, that important issue is one that tinnitus researchers now are beginning to address.

Measured effect sizes, obtained by pre-testing of individual questions, can be used to develop questionnaire items with high responsiveness to treatment-related change.

Applying questionnaire design criteria: an illustrative example

Recently we initiated efforts to develop a new tinnitus questionnaire, in the attempt to maximize construct validity for both diagnostic and treatment-evaluation, using the criteria listed in Table 3. We recognized that it would necessarily represent a compromise between the competing needs for (1) an item list sufficiently comprehensive to provide high construct validity for diagnostic and screening purposes vs. (2) an item list restricted to items with high construct validity for evaluating treatment outcomes. For the planned development process, we set up an 18-member working group of individuals well versed in working with tinnitus patients, a number of whom had participated in developing the questionnaires listed in Table 1. Following recommendations of measurement experts, the purpose of this group was to serve as an expert panel for selecting the content for the new questionnaire (Haynes et al., 1995).

Diagnostic completeness

To address the need for comprehensive evaluation of problematic tinnitus, we solicited responses from our expert panel members in response to a website we created to display all nine of the questionnaires, totaling 175 separate items (Meikle et al., 2005). The web presentation provided a rapid mechanism for surveying the responses of the expert panel members concerning the measurement strengths and/or weaknesses of each item. Each member was asked to independently evaluate each item with regard to (1) its importance for measuring an important aspect or dimension of tinnitus, and (2) its relevance for detecting treatment-related changes in tinnitus. A quantitative rating scheme was then employed to combine all of the expert evaluations and determine the group consensus regarding the important dimensions of tinnitus.

Table 4 summarizes the conclusions regarding the number and identity of dimensions judged important for characterizing clinically significant tinnitus. It can be seen that 13 dimensions were judged important for diagnostic completeness. There was considerable overlap between the various questionnaires, indicating that there was substantial redundancy among the 175 items. It was possible, however, to extract a set of 40 sub-topics or “facets” (represented by 70 of the individual questionnaire items) that were judged potentially sensitive measures of treatment-related change and at the same time provided comprehensive coverage of the content of all 13 dimensions (see listing in column 3 of Table 4). The remaining 105 questionnaire items either duplicated the content of the 70 selected items or were judged less sensitive to treatment change; and a few items were omitted from consideration because they were judged overly negative in flavor (e.g., addressing suicidal thoughts).

Item reduction

For clinical convenience it was necessary to reduce the number of questions to a number smaller than the 70 referred to above. The rationale was that for the prototype questionnaire under construction, 70 items was too many for efficient clinical use. To assist us in reducing the number of items covered in the questionnaire, we were fortunate to have access to unpublished data on effect sizes acquired in a recent clinical trial in which four of the nine questionnaires in Table 1 had been administered to a large sample of patients (Henry et al., 2002b). Many of the 70 candidate items were obtained from those four questionnaires, allowing us to use the information on effect sizes to identify items for which high effect sizes had been observed. For items derived from the other five questionnaires (for which there was no information on effect sizes) we rejected any items having low ratings for their ability to detect treatment-related change, keeping only those items that were judged high enough to function well in treatment outcomes studies. By taking advantage of judgments made by the expert panel in this way, we were able to narrow the list of questionnaire items to a tentative total of thirty-five.

Table 4. Important dimensions of clinically significant tinnitus

Dimension	Number of items related to dimension ^a	Sub-topics or “facets” of the dimension addressed by the various items
1. Intrusiveness	13	Loudness; unpleasantness; uncomfortable in quiet; general discomfort
2. Persistence	15	Percent of time aware; percent of time annoyed; difficulty ignoring tinnitus; loss of “peace and quiet”
3. Emotional effects	52	Depression; anxiety; anger or annoyance; irritability; frustration; feeling upset or bothered
4. Sleep disturbance	12	Difficulty falling or staying asleep
5. Cognitive interference	11	Difficulty concentrating; difficulty focusing attention away from tinnitus; difficulty thinking or remembering
6. Hearing difficulties attributed to tinnitus	13	General interference with hearing by tinnitus; interference with speech comprehension; interference with communication in groups or meetings
7. Somatic or physical complaints attributed to tinnitus	4	Fatigue; headaches due to tinnitus; general feeling of poor health
8. Interference with social activities or enjoyment	18	Harder to interact pleasantly; stress on relationships; interference with social activities; interference with social enjoyment
9. Work interference by tinnitus	4	Difficulty performing work
10. Leisure interference by tinnitus	8	Interference with quiet resting activities; less interested in going out; general interference with leisure
11. Interference with rest and relaxation	5	Reduced ability to relax
12. Impaired quality of life due to tinnitus	11	Reduced enjoyment of life; reduced overall quality of life
13. Reduced sense of control due to tinnitus	2	Difficulty coping with tinnitus; feeling loss of control over tinnitus

^aSeven items did not satisfy the selection criterion of relevance to treatment changes, or were overly negative in content (e.g., referring to suicidal thinking).

Final considerations re-diagnostic completeness

While most dimensions were represented by at least three items (and some dimensions by as many as four items), there were several that were represented by only one or two items. Because of the recommendation that a minimum of three items is required for reliable measurement of a given dimension (Moran et al., 2001), it was therefore necessary to compose eight new items for those dimensions that had not been represented by at least three items. That brought the finished size of the first prototype questionnaire to 43 items.

Item response scaling

The next step in questionnaire construction was to identify the precise format and scaling of the

individual items. The development team for the new questionnaire had been set up specifically to include two specialists with well recognized professional expertise in measurement techniques. Following the recommendations of these two measurement experts, for all of the questions destined for the new prototype we selected a simple question format with responses on a 0–10 scale, as illustrated by the following example item:

Over the past week, how strong or loud has your tinnitus been?

Respondents were asked to circle one number in an 11-point numeric scale printed below the question, with verbal anchors 0 = *not at all strong or loud* at left end, 10 = *extremely strong or loud* at right end. The 11-point scale was chosen because it is relatively high-resolution, easily understandable response format that is familiar to most

respondents. In addition, it provides a high degree of measurement precision for diagnostic and screening purposes, at the same time offering good sensitivity for detecting small changes associated with treatment.

Testing and evaluation of the questionnaire

Clinical testing of the first prototype has recently been completed in a group of more than 300 patients undergoing treatment. The trial has helped by providing information on item effect sizes obtained using the 0–10 measurement scale. The results have been encouraging, in that 34 of the 43 items in the new questionnaire achieved effect sizes ≥ 0.50 , with 15 of those ≥ 0.80 . The discriminative aspects of Prototype 1 were also excellent, with high reliability and construct validity for measuring individual differences in regard to severity and the various negative impacts of tinnitus.

We are now engaged in testing a new, second prototype that was developed by a systematic evaluation of the results obtained using Prototype 1. The purpose of that evaluation was to identify the best-functioning items in Prototype 1, so that we could reduce the respondent burden by reducing the total number of items to 30. The current clinical trial of this second prototype will determine whether this shorter version also achieves high responsiveness to treatment-related changes, while at the same time retaining diagnostic completeness despite the 30% reduction in length. If so, the new prototype will have satisfied the original design goals.

Other issues in designing efficient instruments for tinnitus assessment

Our major aim in this paper has been to highlight certain aspects of questionnaire development that directly affect whether the instrument will function well when used for evaluating treatment outcomes as well as for diagnostic and screening purposes. There are many other details of questionnaire development that are important at early stages of questionnaire design — such as the choice of response metric (e.g., Yes/No; numeric ratings;

Likert-type scales; etc.); phrasing of items (e.g., phrased as questions or as statements that solicit subject’s agreement or disagreement) (Meikle et al., 2003); the total number of items; overall format of the questionnaire, including introductory or explanatory material; and a host of other decisions that need to be made when a questionnaire is being developed. For details about such topics, readers are referred to basic texts on questionnaire development (e.g., Anastasi, 1988).

Several additional topics that are more global in scope are, however, relevant to the present discussion. These are (1) the use of “global” measures of tinnitus and (2) the timeframe of observations for monitoring treatment effects.

Use of global measures of tinnitus

There are times when it is very helpful to have a single, global measure of the impact of tinnitus on individuals participating in a clinical research project. For example, when dealing with a large group of patients, there may be times when it is helpful to stratify patients according to the severity of their tinnitus *before* there are detailed data available from multiple-item questionnaires. It is also helpful to have at least one reliable, well-functioning global item to use in screening candidates for tentative inclusion in a research study. We have found the following global item to be helpful:

How much of a problem is your tinnitus?	
Not a problem.....0	
A small problem.....	1
A moderate problem.....	2
A big problem.....	3
A very big problem.....	4

This item has several advantages: Its wording is clear and unambiguous, and does not require a high level of reading skill; and the 5-level response scale provides a useful level of resolution for stratifying patients into meaningful groups. In addition, we believe that referring to the “problem” aspect of tinnitus tends to focus the individual’s attention on the clinically important aspects of tinnitus rather than on its perceptual qualities as a sensory phenomenon.

The timeframe of treatment observations

Diagnostic and screening evaluations are essentially descriptive, and are typically made at a single point in time such as at intake or when patients return to request professional advice regarding new symptoms or problems. Evaluations of treatment outcomes, in contrast, require varying timeframes depending on how quickly the treatment takes effect, and on how long it can or should be maintained in order to achieve full effects of the treatment. For example, tinnitus-masking effects can be observed immediately, while the patient or research subject is sitting in the testing site; and it is desirable to do so because if masking produces no immediate improvement in tinnitus, then that individual is probably not a candidate for long-term use of tinnitus-masking equipment (Henry and Meikle, 2000; Vernon and Meikle, 2003). On the other hand, the benefit of Tinnitus Retraining Therapy is generally expected to require several months to be achieved, and there is little to be gained from attempting immediate evaluation of its effects (Henry et al., 2002a; Henry et al., 2002b).

For tinnitus masking and other treatments that can have immediately observable effects (such as noninvasive electrical or magnetic stimulation, intratympanic injections of lidocaine or other putative tinnitus-suppressing drugs, and other rapidly-acting agents), clinicians and investigators need to have rapid feedback from the patient. Clearly, questions about the functional effects of the tinnitus treatment (such as improved ability to sleep, reduced difficulties working, reduced feelings of anxiety, or depression) would not be useful as they require days, weeks, or possibly even months before the patient can provide the relevant information. However, changes in tinnitus sensations can be measured immediately, in effect “on-line” as the tinnitus is altered by the treatment (Henry et al., 2004).

Therefore it is important to have reliable outcome measures that focus on rapidly measurable changes in tinnitus sensations. That can be done in a variety of ways—using brief questionnaires, for instance, to evaluate changes in the perceived loudness or other aspects of tinnitus sensations; and other ways include psychoacoustic measures

of tinnitus pitch, loudness matches, maskability, and residual inhibition (Vernon and Meikle, 2003; see reviews by Henry and Meikle, 2000; Tyler, 2000). Numeric-rating scales and visual-analog scales have also been used to obtain rapid indications of the magnitude of tinnitus alterations over time (Vernon, 1981).

At the present time there is little information available to relate sensory changes using numeric or visual analog scales or changes in psychoacoustic measures of tinnitus, to functional or emotional changes such as improved ability to sleep or reductions in irritability and depression. Furthermore, to our knowledge no systematic efforts have been made to evaluate the responsiveness (the sensitivity to change) of either psychoacoustic measures or numeric and visual analog scales for tinnitus. Research to evaluate their sensitivity for registering treatment-related changes of tinnitus is therefore badly needed. Despite these shortcomings, the potential benefits of using such measures are substantial in that besides being rapidly obtainable, they are quantifiable in objectively measurable units (e.g., decibels for tinnitus loudness matches and minimum masking levels; hertz for tinnitus pitch; centimeters for visual analog scales, etc.).

Acknowledgments

We thank the Tinnitus Research Consortium for providing substantial support for the research on which this publication was based. We are also grateful to the Oregon Health and Science University, the Cleveland Clinic Foundation, the Bay Pines and Tampa VA Medical Centers, and the VA RR&D National Center for Rehabilitative Auditory Research (Portland VA Medical Center) for providing clinical and research resources without which the research would not have been possible.

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CHAPTER 50

Consensus for tinnitus patient assessment and treatment outcome measurement: Tinnitus Research Initiative meeting, Regensburg, July 2006

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Abstract: There is widespread recognition that consistency between research centres in the ways that patients with tinnitus are assessed and outcomes following interventions are measured would facilitate more effective co-operation and more meaningful evaluations and comparisons of outcomes. At the first Tinnitus Research Initiative meeting held in Regensburg in July 2006 an attempt was made through workshops to

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gain a consensus both for patient assessments and for outcome measurements. It is hoped that this will contribute towards better cooperation between research centres in finding and evaluating treatments for tinnitus by allowing better comparability between studies.

Keywords: tinnitus; standards; assessment; questionnaires; treatment; outcome; case history

Introduction

Chronic tinnitus, the phantom perception of sound, can be a debilitating and life-altering experience. It affects millions of people in western countries. Despite the enormous social and economic burden tinnitus causes, no well-established specific treatment for this disorder is available. Among the reasons for this unsatisfactory situation are the difficulties in assessing tinnitus as it is a purely self-report subjective phenomenon.

There is widespread recognition that consistency between research centres in the ways that patients with tinnitus are assessed and outcomes following interventions are measured would facilitate more effective co-operation and more meaningful evaluations and comparisons of outcomes. On the other hand most research centres already have long established systems for collecting and assessing data and hence are unable or unwilling to completely change to a different system because so much would be lost.

At the recent (July, 2006) Tinnitus Research Initiative meeting in Regensburg, Germany an attempt was made through workshops to gain a consensus both for patient assessments and for outcome measurements.

It is hoped that this consensus will facilitate cooperation between tinnitus research centres in finding and evaluating treatments for tinnitus and will help achieve more meaningful comparisons between studies.

Consensus for diagnosis and assessment

General statements

There is a need for consensus on assessment and outcome measurement

There is an urgent need for a set of assessment methods to be agreed and utilised by the

international tinnitus research community. This includes assessment of patients with tinnitus and subsequent measurement of outcomes following intervention.

Consistency in assessment of patients with tinnitus will advance the characterisation of their tinnitus into subtypes. As results for most known therapeutic interventions are very inconsistent, the identification of predictors for the effectiveness of various treatments is essential. Characterization of patients with tinnitus into subgroups would be greatly facilitated by consistent assessment of potentially relevant data and may contribute to the development of treatment plans individualised for patients within a subgroup.

An agreement on outcome measurements is a pre-requisite for comparison between treatment studies. This in turn will greatly increase the efficiency of tinnitus research by facilitating meta-analysis and by facilitating communication amongst disciplines using such different treatment interventions as acoustic stimulation, hearing aids, counselling, cognitive behavioural therapy, drug treatments, electrical and magnetic stimulation. Furthermore agreement on outcome measures is required for the engagement of the pharmaceutical industry in tinnitus research.

Any proposed standards must take into account cultural differences, language differences, different health systems, existing databases and existing routines

Even though a high degree of conformity is desirable, recognition has to be given to intrinsic limitations to achieving this. Comparability of questionnaires is limited by the sensitivity of some items to cultural differences and language. Other factors such as costs and the organisational structures of health care systems and facilities have a marked impact on routines used in the assessment of tinnitus patients. Some tinnitus centres already

have very large databases built up through their existing systems. Such limitations by established practice have to be accommodated. There was consensus that wide acceptance can only be achieved if any proposed new instrument is as compatible as possible with existing routines.

The consensus achieved at Regensburg is an agreement on minimum requirements

It was agreed that a “*Consensus for Patient Assessment and Treatment Outcome Measurement*” had to be limited to a set of core items and could only represent a minimum requirement. A consensus agreement cannot claim to meet optimum expectations or to represent an ideal. It documents what *all participants agree is necessary*. Many of the participants considered that additional information is required about patients and will collect and assess this additional information. However because of the limitations identified in the previous section there is no consensus about such additional information.

Agreement was achieved on which aspects should be assessed

Consensus was achieved on which aspects of tinnitus and related items should be assessed while retaining flexibility on how they can be assessed. This strategy allows both consistency and compatibility with routines already existing in different centres.

Prioritisation of items

Prioritisation of items was agreed as a further strategy to affect a compromise between consistency and feasibility. Items were prioritised according to their level of importance. Items assessed as level A are considered *essential*, items assessed as level B are *highly recommended* and items assessed as level C *might be of interest* in some contexts. This prioritisation of items is based on the understanding that the consensus represents an agreement on minimum requirements and not on optimal expectations.

Applicability

These consensus agreements for patient assessment and outcome measurements should be applicable and useful to all clinicians and researchers dealing with patients with tinnitus. They are a step towards more comprehensive agreements. They may also be helpful to those advising Tinnitus Research Initiative and other funding organisations about research applications.

Consensus for patient assessments and treatment outcome measurements (TRI workshop 2006)

This consensus was developed during workshops at the TRI meeting in Regensburg July 2006. A provisional consensus summary was then sent to all workshop participants giving them the opportunity to check whether this summary accurately reflected the agreements reached during the workshops. Feedback was received from all authors and the consensus summary modified slightly as a result (see [Table 1](#)).

Physical examination

There was agreement that an otologic examination by a specialist is an essential part of tinnitus patient assessment. Otologic examinations are performed by otolaryngologists and also by a variety of other health professionals depending on the health system. The profession of the specialist has not been specified.

For assessment of potential somatosensory components of a patient's tinnitus examination of the neck (including range of motion, tenderness and muscle tension) is considered essential. Examination of temporomandibular function (including dental problems) is highly recommended.

Audiologic assessment

Diagnostic pure tone audiometry (up to 8 kHz) for the assessment of hearing loss is considered necessary in every patient. High-frequency audiometry up to 12 kHz is highly recommended, as are immittance audiometry, assessment of otoacoustic

Table 1. Consensus for patient assessment and outcome measurements (TRI workshop 2006)

In each category recommendations are ordered according to their level of significance

A: Essential B: Highly recommended C: Might be of interest

Patient Assessment

Physical examination

A: Otologic examination by a specialist

A: Examination of the neck (range of motion, tenderness, muscle tension...)

B: Examination of the temporomandibular function

Audiologic assessment

A: Audiometry (pure tone threshold; up to 8 kHz)

B: Immitance audiometry

B: High-frequency audiometry (at least up to 12 kHz)

B: Otoacoustic emissions

B: Loudness discomfort level

C: Auditory evoked potentials

Psychophysics measures of tinnitus

B: Loudness match

B: Pitch match

B: Maskability (MML)

B: Residual inhibition

Case history

A majority of participants preferred a questionnaire to be filled in by the patient (with access to someone for clarification) rather than at a structured interview. This was not a consensus. It was agreed that as a first step towards consensus a list of those items common to most existing questionnaires should be made. A first attempt to extract such a list is attached.

Questionnaires

A: Validated questionnaire for the assessment of tinnitus severity, which at present can be THI, THQ, TRQ or TQ (it was agreed that in the future a better and more widely validated questionnaire was required)

B: Assessment of tinnitus severity by additional questionnaires, and especially by the THI because it is believed that THI is validated in most languages

C: Assessment of depressive symptoms (e.g. BDI)

C: Assessment of anxiety (e.g. STAI)

C: Assessment of quality of life (e.g. WHODAS II)

C: Assessment of insomnia (e.g. PSQI)

Outcome Measurements

A: Validated questionnaire for the assessment of tinnitus severity, which at present can be THI, THQ, TRQ or TQ (it was agreed that in the future a better and more widely validated questionnaire was required)

B: Assessment of tinnitus severity by additional questionnaires, and especially by the THI because it is believed that THI is validated in most languages

C: Assessment of depressive symptoms (e.g. BDI)

C: Assessment of anxiety (e.g. STAI)

C: Assessment of quality of life (e.g. WHODAS II)

C: Assessment of insomnia (e.g. PSQI)

C: Tinnitus loudness match

C: Maskability (MML)

C: Objective measurement of brain function (functional imaging, electrophysiology)

Abbreviations

KHz

Kilohertz

dB

Decibel

SL

Sensation level

MML

Minimal masking level

THI

Tinnitus Handicap Inventory (Newman et al., 1998)

THQ

Tinnitus Handicap Questionnaire (Kuk et al., 1990)

TRQ

Tinnitus Reaction Questionnaire (Wilson et al., 1991)

TQ

Tinnitus Questionnaire (Hallam et al., 1988)

BDI

Beck Depression Inventory (Beck and Steer, 1984)

STAI

State Trait Anxiety Inventory (Spielberger et al., 1970)

WHODAS

WHO Disability Assessment Schedule (McArdle et al., 2005)

PSQI

Pittsburgh Sleep Quality Index (Buysse et al., 1989)

emissions and loudness discomfort levels. The measurement of auditory evoked potentials might be of interest, especially for excluding vestibular schwannoma if appropriate organ imaging is not available.

Psychophysical measures of tinnitus

Psychophysical measures are not considered essential, as neither the loudness match nor other psychoacoustic measures bear a consistent relationship to the severity or perceived loudness of tinnitus (Henry and Meikle, 2000). Nevertheless quantification can yield important information in tinnitus research and therefore the assessment of pitch match, loudness match, maskability and residual inhibition are highly recommended. Furthermore loudness match and maskability can be of interest as *outcome measures* in treatment trials.

Concerns were raised that results of psychoacoustic measurements depend on the protocols used for the assessments. Standardisation of assessment procedures, even if highly desirable, is very difficult to achieve, because it would require specialized instrumentation, which is not available to most audiologists. The workshop participants recommend thorough documentation of the techniques used for psychoacoustic measures.

Case history questionnaires

Information about the history and descriptive characteristics of the patient's tinnitus or tinnitus related conditions could be obtained by questionnaires or by structured interviews. A large majority of the workshop participants agreed that these data are better obtained by a questionnaire both for logistical reasons and to achieve greater reliability. It was suggested that if a patient is uncertain how to answer a question this should be clarified during the subsequent clinical interview. Only a few case history questionnaires have been published (Newman and Sandridge, 2006). However, most clinicians and researchers have developed their own questionnaires (and/or structured interviews) in which they include those questions, which they consider important and relevant. Based

on this information many centres have developed databases, which include large numbers of patients presenting at their clinics over several decades (e.g. Meikle, 1997). This approach does not facilitate comparison between centres.

In order to achieve comparability of data it was agreed that an item list for case history questionnaires should be developed which should include those items common to many of the questionnaires (and structured interviews) in current use. Due to time constraints these items were not identified during the workshops. Two of the authors (BL, RG) have sorted through a considerable variety of case history questionnaires and identified a set of items common to most of them, which might therefore be regarded as essential (level A) and could be expected to be included in all questionnaires. They also identified additional items common to many questionnaires, which could be regarded as highly desirable (level B). These items are listed as a starting point for further discussion and were sent to all workshop participants. Based on feedback from the participants the "*Items list*" for *tinnitus case history questionnaires* (see Table 2) has been compiled. This list consists of 14 essential (level A) items and 21 highly desirable (level B) items.

These 35 items have also been shown in the form in which they appear in one particular case history questionnaire (Tinnitus Sample Case History Questionnaire, TSCHQ, Table 3). This could be used as a resource of how these items might be expressed.

This approach of identifying items with high levels of use and hence of importance achieves compatibility with existing systems for case history data collection. Existing case history questionnaires can be modified by adding missing items. The TSCHQ (Table 3) could be used in its entirety or modified.

Questionnaires as instruments for measuring tinnitus and related disorders

Several questionnaires have been developed for the "measurement" of tinnitus severity. These were mainly designed for screening and diagnostic purposes. Most of these attempt to quantify a combination of tinnitus related distress, disability and handicap resulting in a large overlap of their items.

Table 2. "Items list" for tinnitus case history questionnaires

The items 1, 2, 4, 5, 6, 8, 9, 12, 16, 19, 21, 26, 27, 28 are considered as essential (Category A) all other items are regarded as highly desirable (Category B)

Background

1. Age.
2. Gender.
3. Handedness.
4. Family history of tinnitus (parent, sibling, children).

Tinnitus history

5. Initial onset. Time?
6. Initial onset. Mode? Gradual or abrupt?
7. Initial onset. Associated events? Hearing change, Acoustic trauma, Otitis media, Head trauma, Whiplash, Dental Treatment, Stress, Other.
8. Pattern. Steady? Pulsatile? Other?
9. Site. Right ear? Left ear? Both ears? (symmetrical?) Inside head?
10. Intermittent or constant?
11. Fluctuant or non-fluctuant?
12. Loudness. Scale 1–100. At worst & at best?
13. Quality. Own words/give a list of choices.
14. Pure tone or noise? Uncertain/polyphonic?
15. Pitch. Very high? High? Medium? Low?
16. Percentage of awake time aware of tinnitus?
17. Percentage of awake time annoyed by tinnitus?
18. Previous tinnitus treatments (no, some, many)?

Modifying influences

19. Natural masking? Music, everyday sounds, other sounds?
20. Aggravated by loud noise?
21. Altered by head and neck movement or touching of head or upper limbs (specification of the respective movements)?
22. Daytime nap. Worse? Better? No effect?
23. Effect of nocturnal sleep on daytime tinnitus?
24. Effect of stress?
25. Effect of medications? Which?

Related conditions

26. Hearing impairment?
27. Hearing aids (no, left ear, right ear, both ears; effect on tinnitus)?
28. Noise annoyance or intolerance?
29. Noise induced pain?
30. Headaches?
31. Vertigo/dizziness?
32. Temporomandibular disorder?
33. Neck pain?
34. Other pain syndromes?
35. Under treatment for psychiatric problems?

As an example of how the above items can be expressed for patients to complete see Table 3.

Among the most widely used are the Tinnitus Handicap Inventory (THI) (Newman et al., 1998), the Tinnitus Handicap Questionnaire (THQ) (Kuk et al., 1990), the Tinnitus Questionnaire (Hallam et al., 1988) and the Tinnitus Reaction

Questionnaire (TRQ) (Wilson et al., 1991). Even though these instruments were not specifically designed to be sensitive to treatment related changes, all of them have been used as outcome measurers in clinical trials.

Table 3. Tinnitus Sample Case History Questionnaire (TSCHQ)

TINNITUS SAMPLE CASE HISTORY QUESTIONNAIRE (TSCHQ)	
NAME:	DATE:
DATE OF BIRTH:	

1. Age:	
2. Gender:	<input type="checkbox"/> Male <input type="checkbox"/> Female
3. Handedness	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Both Sides
4. Family history of tinnitus complaints	
<input type="checkbox"/> YES if YES: <input type="checkbox"/> parents <input type="checkbox"/> siblings <input type="checkbox"/> children <input type="checkbox"/> NO	

5. Initial onset: When did you first experience your tinnitus? _____	
6. How did you perceive the beginning? <input type="checkbox"/> Gradual <input type="checkbox"/> Abrupt	
7. Was the initial onset of your tinnitus related to:	
<input type="checkbox"/> loud blast of sound <input type="checkbox"/> whiplash <input type="checkbox"/> change in hearing <input type="checkbox"/> stress	
<input type="checkbox"/> head trauma <input type="checkbox"/> others _____	
8. Does your tinnitus seem to PULSATE ?	
<input type="checkbox"/> YES with heart beat <input type="checkbox"/> YES, different from heart beat <input type="checkbox"/> NO	

Table 3. (Continued)

<p>9. Where do you perceive your tinnitus</p> <p> <input type="checkbox"/> right ear <input type="checkbox"/> left ear <input type="checkbox"/> both ears, worse in left <input type="checkbox"/> both ears, worse in right <input type="checkbox"/> both ears, equally <input type="checkbox"/> inside the head <input type="checkbox"/> elsewhere </p>			
<p>10. How does your tinnitus manifest itself over time?</p> <p> <input type="checkbox"/> intermittent <input type="checkbox"/> constant </p>			
<p>11. Does the <i>LOUDNESS</i> of the tinnitus vary from day to day?</p> <p> <input type="checkbox"/> YES <input type="checkbox"/> NO </p>			
<p>12. Describe the <i>LOUDNESS</i> of your tinnitus using a scale from 1-100.</p> <p>(1 = <i>VERY FAINT</i>; 100 = <i>VERY LOUD</i>)</p> <p>_____ (1 – 100)</p>			
<p>13. Please describe in your own words what your tinnitus usually sounds like:</p> <p>_____</p> <p>The following list gives examples of some possible sensations, feel free to use other terms as well: hissing, ringing, pulsing, buzzing, clicking, cracking, tonal (like a dial tone or other kinds of tones), humming, popping, roaring, rushing, typewriter, whistling, whooshing.</p>			
<p>14. Does your tinnitus more sound like a tone or more like noise:</p> <p> <input type="checkbox"/> tone <input type="checkbox"/> noise <input type="checkbox"/> crickets <input type="checkbox"/> other </p>			

Table 3. (Continued)

<p>15. Please describe the PITCH of your tinnitus:</p> <p> <input type="checkbox"/> very high frequency <input type="checkbox"/> high frequency <input type="checkbox"/> medium frequency <input type="checkbox"/> low frequency </p>
<p>16. What percent of your total awake time, over the last month, have you been aware of your tinnitus ? For example, 100% would indicate that you were aware of your tinnitus all the time, and 25% would indicate that you were aware of your tinnitus ¼ of the time</p> <p>_____ % (Please write in a single number between 1 and 100.)</p>
<p>17. What percent of your total awake time, over the last month, have you been annoyed, distressed, or irritated of your tinnitus ?</p> <p>_____ % (Please write in a single number between 1 and 100.)</p>
<p>18. How many different treatments have you undergone because of your tinnitus ?</p> <p> <input type="checkbox"/> none <input type="checkbox"/> one <input type="checkbox"/> several <input type="checkbox"/> many </p>
<p>19. Is your tinnitus reduced by music or by certain types of environmental sounds such as the noise of a waterfall or the noise of running water when you are standing in the shower ?</p> <p> <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> don't know </p>
<p>20. Does the presence of loud noise make your tinnitus worse?</p> <p> <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> I don't know </p>
<p>21. Does any head and neck movement (e.g. moving the jaw forward or clenching the teeth), or having your arms/hands or head touched, affect your tinnitus ?</p> <p> <input type="checkbox"/> YES <input type="checkbox"/> NO </p>

Table 3. (Continued)

<p>22. Does taking a nap during the day affect your tinnitus?</p> <p> <input type="checkbox"/> worsens my tinnitus <input type="checkbox"/> reduces my tinnitus <input type="checkbox"/> has no effect </p>											
<p>23. Is there any relationship between sleep at night and your tinnitus during the day ?</p> <p> <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> I don't know </p>											
<p>24. Does stress influence your tinnitus?</p> <p> <input type="checkbox"/> worsens my tinnitus <input type="checkbox"/> reduces my tinnitus <input type="checkbox"/> has no effect </p>											
<p>25. Does medication have an effect on your tinnitus?</p> <table border="1"> <thead> <tr> <th>Medication</th> <th>Effect / Details</th> </tr> </thead> <tbody> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> <tr><td> </td><td> </td></tr> </tbody> </table>		Medication	Effect / Details								
Medication	Effect / Details										
<p>26. Do you think you have a hearing problem?</p> <p> <input type="checkbox"/> YES <input type="checkbox"/> NO </p>											
<p>27. Do you wear hearing aids?</p> <p> <input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Both <input type="checkbox"/> None </p>											
<p>28. Do you have a problem tolerating sounds because they often seem much too loud ? That is, do you often find too loud or hurtful sounds which other people around you find quite comfortable ?</p> <p> <input type="checkbox"/> Never <input type="checkbox"/> Rarely <input type="checkbox"/> Sometimes <input type="checkbox"/> Usually <input type="checkbox"/> Always </p>											

Table 3. (Continued)

<p>29. Do sounds cause you pain or physical discomfort ?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> I don't know</p>
<p>30. Do you suffer from headache?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>31. Do you suffer from vertigo or dizziness?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>32. Do you suffer from temporomandibular disorder?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>33. Do you suffer from neck pain</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>34. Do you suffer from other pain syndromes?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>35. Are you currently under treatment for psychiatric problems ?</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>

It is unrealistic to expect everyone to agree to use the same one of these questionnaires as primary outcome measure in their clinical trials. First, each of these questionnaires has its strengths and weaknesses. Their sensitivities may vary depending on the therapy used and they

sometimes produce results different from each other. Secondly, new questionnaires specifically designed to evaluate treatment related changes, will emerge in the near future. Thirdly, all of these questionnaires have been developed in the English language and only some of them have

been translated and validated in some other languages.

It was generally agreed that a questionnaire is required which is specifically designed for the assessment of treatment outcomes, and which is validated in many languages and in many cultural and socio-economic groups.

The consensus agreement is that at the present time one validated questionnaire, which can be THI, THQ, TRQ or TQ, is an essential part of *patient assessment*. Therapeutic trials should use one of these questionnaires also as *outcome measurement*. Assessment of tinnitus severity with at least one additional questionnaire is highly recommended. A majority of the participants favoured the THI as an additional questionnaire because the THI is thought to be validated in the largest number of languages (Zachariae et al., 2000; Herraiz et al., 2001; Paula Erika et al., 2005; Kleinjung et al., 2007) and may thus facilitate comparability between studies.

Consensus was that assessments of tinnitus related disorders such as depression, anxiety and insomnia are of interest in some contexts. These can be assessed by specific validated instruments such as the Beck Depression Inventory (BDI) (Beck and Steer, 1984) for the quantification of depressive symptoms, the State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1970) for anxiety and the Pittsburgh Sleep Quality Index (Buysse et al., 1989) for insomnia. To assess effects on quality of life the WHO Disability Assessment Scale (WHO DAS II) can be used. It was noted that this patient self-rating scale of functioning has been shown to be especially suitable as an outcome measure for the treatment of hearing disorders (McArdle et al., 2005).

Objective measures

An increasing amount of data from pilot studies indicates considerable potential for a variety of electrophysiologic and neuroimaging methods to assess alterations in brain structure and function in patients with tinnitus. None of the participants considered any of these to be an established diagnostic tool. However, there was recognition that behavioural tests are insufficient and that the identification of neurobiological changes that can be measured objectively is highly desirable.

Acknowledgements

The authors wish to thank Ulli Soltani for organisational assistance.

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